

- ORGAN TRANSPLANT IMMUNOLOGY
- Objectives
- Discuss the concept of transplantation
- Classify the different types of transplant
- Explain the histocompatibility antigens
- Explain the importance of histocompatibility testing in transplantation
- Explain the graft versus host rejection
- Organ transplantation
- **Organ transplantation** is the moving of an organ from one body

to another or from a donor site to another location on the patient's own body, for the purpose of replacing the recipient's damaged or absent organ

- Transplantation immunology - sequence of immunological reactions that occur after transplant
- A major limitation to the success of transplantation is the immune response of the recipient to the donor tissue.
- Rejection
- A major barrier to transplantation is the process of *rejection*, in which

the recipient's immune system recognizes the graft as being foreign and attacks it

- Self tolerance
- During fetal life ,within the thymus, a very important processes called thymic education occurs.
 - Immune cells that react with “self” antigens are killed by a process called apoptosis
 - The removal of these self-reactive cells, a process called negative selection, results in tolerance to our own proteins, ie, self-tolerance, and prevents autoimmune reactions
- Types of transplant

- Autograft
- Autograft is self-tissue transferred from one body site to another in the same individual.
- Accepted
- Isograft
- Isograft is tissue transferred between genetically identical individuals.
- Accepted
- Allograft
- is tissue transferred between genetically different members of the same species.
- Rejected unless given immunosuppressant drugs
- Xenograft

- Xenograft is tissue transferred between different species
- Rejected
- Major histocompatibility proteins
- The reason for rejection of a transplanted organ are glycoproteins on cell surfaces called major histocompatibility proteins(MHC)
- If the MHC proteins on the donor's cells differ from those on the recipient's cells, an immune response occurs in the recipient
- Every cell in the body are covered by these histocompatibility proteins and except for identical twins they are different in each individuals

- Also called human leukocyte antigens (HLA)
- The genes encoding these proteins are inherited as 2 sets (one from father, one from mother)
- One set is called haplotype
- The genes for the MHC proteins located on the short arm of chromosome 6.
- **There are four general groups of HLA**, they are HLA-A, HLA-B, HLA-C (encode class I MHC proteins) and HLA-DR (encode class II MHC proteins). There are many different specific **HLA** proteins within each of these three groups. (For example, there are 59 different

HLA-A proteins, 118 different HLA-B and 124 different HLA-DR!) Each of these **HLA** has a different numerical designation, for example, you may have HLA-A1, while some one else might have HLA-A2.

- 25% chance of sharing both haplotypes, 50% chance of sharing one haplotype and 25% chance of sharing no haplotype among siblings
- Mechanism of immune rejection
- Direct pathway
 - T cells of the recipient recognize donor class I & II MHC proteins on the surface of antigen presenting cells(dendritic cells,macrophages etc.) in the graft.

- CD8+ T cells recognize class I MHC proteins and differentiate into active Cytotoxic T cells secreting enzymes that destroy donor cells
- CD4+ helper T cells recognize class II molecules → proliferate to activated CD4+ T cells. → activated CD4+ T cells secrete cytokine that activate macrophages → activated macrophages destroy graft cells
- Mechanism of Immune rejection
- Indirect pathway
 - Donor MHC molecules are shed → picked up, processed, and presented by the *host's* own APCs. This form of recognition mainly activates DTH pathways.
 - The indirect pathway is also involved in the production of antibodies against graft alloantigens

- HLA match
- The HLA “match” is the number of HLA molecules that any two people have in common. HLA matching is usually based on 10 HLA molecules. The more molecules two people share, the better the match
- HLA matching in laboratory
- Serological techniques
 - Donor and recipient blood cells are mixed with known serum containing the anti-HLA antibodies. If the antibodies recognize their corresponding antigen then complement activation occurs and the cell will be lysed
- Molecular techniques

- Gene sequencing with PCR based techniques
- Cross match testing
- Blood from the donor and recipient are mixed. If the recipient's serum has antibodies that attack and kill the donor white cells, the crossmatch is considered positive. If the crossmatch is negative, the pair is considered compatible.
- To prevent hyperacute rejection
- Clinical phases of rejection
- Hyperacute rejection
 - occurs within minutes to a few hours after transplantation
 - Pre-existing antibodies in the host circulation bind to donor endothelial antigens in blood vessels generated

because of previous
transplants,transfusions or
pregnancies

- Massive heamorrhages and
thrombosis

- Clinical phases of rejection
- Acute rejection
 - Vascular and parenchymal injury
mediated by T cells and antibodies
that usually begin after the first week
(10-30 days)of transplantation if there
is no immunosuppressant therapy
 - Incidence is high (30%) for the first 90
days

- Clinical phases of rejection

- Chronic rejection
 - present clinically late after transplantation (months to years)
 - Dominated by arteriosclerosis, this type is probably caused by T-cell reaction and secretion of cytokines that induce proliferation of vascular smooth muscle cells, associated with parenchymal fibrosis
 - Difficult to manage even with immunosuppressant drugs

- Graft versus host reaction
- Caused by the reaction of mature T-cells in the grafted tissue (from donor) with antigens of the recipient

- Usually occurs with bone marrow transplant(rich in T-cells)
- Graft versus host disease
- Acute GVHD(first 100 days)
 - Characterized by epithelial cell death usually in the
 - skin,
 - diffuse maculopapular rash
 - GI tract
 - severe diarrhea, abdominal pain, nausea, and vomiting
 - Liver
 - Increased bilirubin
- Chronic GVHD(after 100 days)
 - Characterized by atrophy and fibrosis of one or more of these same target organs as well as the lungs
- Prevention of transplant rejection

- Immunosuppressant drugs
- Prognosis
- 2010 survey 5 year post kidney transplant survival rate with one haplotype match was more than 90% ; no haplotype match 80% with immunosuppressant treatment.
- Best results with corneal transplant