Transplantation
Immunology
- **Transplantation**: When an organ or tissue becomes irreparably damaged, or congenitally defective or absent, transplantation or grafting becomes necessary for the restoration of function.

- Tissue or organ transplanted is k/a *transplant* or *graft*.

- **Donor**: Individual from whom the transplant is obtained

- **Recipient**: Individual to whom the transplant is applied.
History

• Earliest application of transplantation appears to have been skin grafting for reconstruction of a severed nose, using the patient’s own skin flaps- a technique described in the *Shushruta Samhita*.

• Alexis Carrel in 1908, interchanged both kidneys in a series of nine cats; some cats maintained urinary output for 25 days.

• 1935- first human kidney transplant by Russian surgeon attempted, but failed.

• Immunological basis for the rejection of exogenous grafts was proved by Medawar and his colleagues in 1940s.
Timeline of successful transplants

- 1905: First successful cornea transplant
- 1954: First successful kidney transplant by Joseph Murray
- 1966: First successful pancreas transplant
- 1967: First successful liver transplant by Thomas Starzl
- 1967: First successful heart transplant by Christian Barnard (Cape Town, South Africa)
Timeline of successful transplants

• 1981: First successful heart/lung transplant by Bruce Reitz.

• 1998: First successful live-donor partial pancreas transplant by David Sutherland.

• 2005: First successful partial face transplant.

• 2008: First baby born from transplanted ovary.

• 2010: First full facial transplant, by Dr Joan Pere Barret and team (Hospital Universitari Vall d'Hebron on July 26, 2010 in Barcelona, Spain)
Classification

- Based on antigenic relationship b/w donor and recipient
  - Autograft
  - Isograft
  - Allografts
  - Xenografts
Autograft: Within an individual

Isograft: Identical Twins

Allograft: Non-Identical

Xenograft: Between species
Immunology of Graft rejection

- Grafts between ordinary brothers and sisters or between parents and offsprings, or even between dissimilar twins are known as allografts.

- Allografts are the most common type of transplantation & survive longer than xenografts but are ultimately rejected.
Major Histocompatibility Complex

• Genes mediating graft rejection in mice are called Histocompatibility genes or H genes or H loci.

• Strongest locus is k/a Major histocompatibility complex (MHC) and weaker loci are called as minor histocompatibility loci.

• MHC in humans is k/a Human leucocyte antigen(HLA) complex.
Major Histocompatibility Complex

- Genes coding for HLA antigens found on short arm of 6th pair of chromosome.
- MHC genes are contained within 4 HLA loci- A, B, C & D with different alleles at each of them like HLA-A(24), B(52) and C(11) loci.
- **Nomenclature:** Alleles are assigned the letters signifying the locus followed by a number signifying the allele e.g. HLA-A10 implies HLA allele number 10 belonging to locus A.
- 3 classes of MHC genes, Class I, II and III are located in these HLA loci.
### Human HLA complex

<table>
<thead>
<tr>
<th>Complex</th>
<th>HLA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MHC class</strong></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>III</td>
<td>I</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
</tr>
<tr>
<td>DP</td>
<td>DQ</td>
</tr>
<tr>
<td>C4, C2, BF</td>
<td>B</td>
</tr>
<tr>
<td><strong>Gene products</strong></td>
<td></td>
</tr>
<tr>
<td>DP αβ</td>
<td>DQ αβ</td>
</tr>
<tr>
<td>C' proteins</td>
<td>TNF-α</td>
</tr>
<tr>
<td>HLA-B</td>
<td>HLA-C</td>
</tr>
</tbody>
</table>
MHC class I molecules

- Products of HLA-A, HLA-B and HLA-C loci
- Class I antigens - membrane bound glycoprotein composed of 2 polypeptide chains.
- Larger polypeptide chain (encoded by HLA-A, B and C regions) has 5 structural domains
  - 3 external globular domains (α1, α2 and α3), a transmembrane portion and a short cytoplasmic tail.
  - Smaller polypeptide chain - β2 microglobulin (encoded by genes on Chr. 2); bound to α3 domain on outer side
- Present on all nucleated cells except ova, sperms and amniotic cells.
- Involved in recognition of target cells by cytotoxic T cells (Tc).
The diagram illustrates the structure of Class I and Class II molecules, which are integral membrane proteins. Each molecule consists of several domains:

- **Membrane-distal domains**
- **Membrane-proximal domains** (Ig-fold structure)
- **Transmembrane segment**
- **Cytoplasmic tail**

Class I molecules are characterized by an alpha-helical transmembrane region and a peptide-binding cleft in the alpha-2 domain. Class II molecules, on the other hand, contain an additional beta chain (beta-1 and beta-2) that forms the peptide-binding cleft with the alpha chain (alpha-1) of the Class II molecule.
MHC class II molecules

- Encoded by HLA-DP, DQ and DR loci (within HLA-D region)
- Glycoproteins consisting of two polypeptide chains (α and β), inserted into the cell membrane.
- Each chain composed of 2 extracellular domains (α1, α2 and β1, β2), a transmembrane portion and a cytoplasmic tail.
- Limited distribution - found on immunologically reactive cells; B lymphocytes, macrophages, monocytes and activated T lymphocytes.
- Both class I and II molecules are involved in cell-cell interaction in the generation and regulation of immune responses.
MHC class III molecules

- Located between class I and II
- Genes encode for the complement components of classical (C2 and C4) and alternative (properdin, Factor B) pathway.
Minor histocompatibility antigens

• Little known about minor histocompatibility antigens (MiHA) in man.
• Role in GVHD and a unique target organ involvement.
• Wide but variable tissue expression pattern, but all are expressed in hematopoietic cells.
• Preponderance of MiHA expression on hematopoietic cells might account for making the host immune system a primary target for GVH response
MHC restriction

- Limitation imposed upon activation of an immune response, unless antigen presentation occurs in association with either class I or class II MHC antigen.
- Foreign antigen + class I MHC $\rightarrow$ recognized by Tc $\rightarrow$ expansion of Tc cells
- Foreign antigen + class II MHC $\rightarrow$ recognized by $T_h$ $\rightarrow$ expansion of $T_h$ cells
MHC restriction

• IL-1 produced by APCs promote both proliferation and differentiation responses to Tc and $T_h$ cells and IL-2 produced by activated $T_h$ cells $\rightarrow$ clonal expansion of Tc cells $\rightarrow$ recognize and destroy target cells

• In addition to transplantation reactions, MHC is involved in immune surveillance e.g., viral infections
Allograft rejection

• **First set reaction:** occurs when graft applied for the first time.

• **Second set reaction:** occurs when an individual has rejected a graft by first set reaction & is again exposed to the graft from the same donor leading to hyperacute or immediate rejection.
Mechanism of allograft rejection

- In *first set reaction*, graft antigen travel to lymph nodes where they activate T cells giving rise to expanded clones of specific Tc, Th cells.
- Tc enter circulation directly and destroy grafted tissue by repeated cell to cell toxicity.
Mechanism of allograft rejection

- **Second set reaction**: due to immunological memory, blood vessels of graft are destroyed as soon as they are established.
- Tc cells, circulating complement fixing antibodies and NK cells contribute to graft rejection.
- Infiltrating neutrophils, macrophages and Tc cells irreversibly reject the foreign tissue transplanted for second time.
Mechanism of allograft rejection

- Cells of an individual express a unique set of membrane antigens called histocompatibility antigens, defining a person’s cell type as do fingerprints.
- Information for synthesis stored in histocompatibility genes.
- Discriminate self from non-self.
- Only grafts having complete identity between donor and recipient genetic constitution survive.
Mechanism of allograft rejection

- **Cell mediated (major role)** and humoral mediated (minor role)
- **Cell mediated** graft rejection has two stages:
  i) Sensitization stage - CD4 and CD8 T cells recognize alloantigens and proliferate in response

  ii) Effector stage - mediated by following mechanisms:
    ✓ Delayed type hypersensitivity
    ✓ CTL-mediated cytotoxicity
    ✓ Antibody-plus-complement lysis
    ✓ ADCC
Different patterns of graft rejection

<table>
<thead>
<tr>
<th>Type of rejection</th>
<th>Time taken</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Minutes-hours</td>
<td>Preformed anti-donor antibodies and complement</td>
</tr>
<tr>
<td>Accelerated</td>
<td>Days</td>
<td>Reactivation of sensitised T cells</td>
</tr>
<tr>
<td>Acute</td>
<td>Days-weeks</td>
<td>Primary activation of T cells</td>
</tr>
<tr>
<td>Chronic</td>
<td>Months-years</td>
<td>May be antibodies, immune complexes, slow cellular reactions, recurrence of disease</td>
</tr>
</tbody>
</table>
Acute rejection

- Occurs within 10 days; dense cellular infiltration
- APCs in graft, mostly dendritic cells (MHC Class II) present antigen to recipient lymphocytes
- If passenger cells absent, APCs of recipient have to process and present the antigen.
- Activated $T_h$ cells produce IL-2 which help in activation and proliferation of B cells and Tc cells and mediate ADCC and T cell cytotoxicity.
- T/t- 1. High dose corticosteroids
  2. Antilymphocyte antibodies
  3. Monoclonal antibodies to CD3 T cells and against IL-2 receptor.
Hyper acute rejection

- Rejection within minutes; sludging of red cells and microthrombi in blood vessels
- Occurs in presensitized individuals, sensitised with preexisting Abs to blood group antigens/MHC class I Ag of donor through blood transfusion.
- Ag-Ab complex activates complement $\Rightarrow$ activation of clotting pathway $\Rightarrow$ microthrombi formation $\Rightarrow$ severe ischaemia and necrosis of the graft.
- T/t- No effective T/t.
Steps in the hyperacute rejection of a kidney graft.

1. Pre-existing host antibodies are carried to kidney graft.
2. Antibodies bind to antigens of renal capillaries and activate complement (C⁻).
3. Complement split products attract neutrophils, which release lytic enzymes.
4. Neutrophil lytic enzymes destroy endothelial cells; platelets adhere to injured tissue, causing vascular blockage.

FIGURE 21-7
Accelerated reaction

- Transplantation of a second graft, which shares a significant number of antigenic determinants with the first one, results in a rapid (2 - 5 days) rejection.
- Due to presence of T-lymphocytes sensitized during the first graft rejection.
- Mediated by immediate production of lymphokines, activation of monocytes and macrophages, and induction of cytotoxic lymphocytes.
Chronic rejection

- Rejection of graft, months-years after transplantation; narrowing of vascular arterial lumen due to growth of endothelial lining of vascular bed.
- Both humoral and cell mediated response
- IL-1 (monocytes) and platelet derived GF (platelets and endothelial cells) → proliferation of endothelial cells.
- Initially proliferation is reversible, but later progress to fibrotic changes → graft ischaemia and loss of function.
- T/t- No effective T/t
Prevention and therapy of allograft rejection

- Tissue typing
- Immunosuppressive therapy
- Induction of immune tolerance
Histocompatibility Testing

• For matching of donor and recipient following procedures are undertaken:

1. ABO grouping: 1st step in transplantation. If discrepancy in ABO blood group, use of prospective donor’s tissue is absolutely contraindicated.

2. Tissue Typing(detection of MHC antigen): Class I antigen are detected by means of sera so k/a serologically defined antigens.
Histocompatibility Testing

- Antisera used can be obtained from
  - Multiparous women
  - Individuals receiving multiple blood transfusions
  - Individuals who have received and rejected the grafts
  - Volunteers who have been immunized with cells from another individual with a different haplotype
Histocompatibility Testing

a. **Lymphoagglutination test**: donor and recipient lymphocytes mixed with a panel of specific antisera, agglutination of lymphocytes is seen with specific antiserum.

b. **Lymphocytotoxicity test**: donor and recipient lymphocytes are incubated with a panel of specific antisera directed against class I MHC antigens → addition of complement → lysis of the cell with specific antiserum.

c. **Mixed lymphocyte culture (MLC)**: for matching class II MHC antigens. Irradiated donor and recipient lymphocytes mixed together in a tube containing radioactive DNA precursor.

   If class II antigens are foreign → responder cells stimulated to divide (incorporate the radioactive precursor) → radioactivity measured and quantified.
(a) HLA–A allele 2
Donor cell

HLA–A allele 1
Recipient cell

Antibody to HLA–A allele 2

Complement

Cells become leaky

Dye (trypan blue or eosin Y)

Dye taken up

No lysis

Dye excluded
(b) Antibody to different HLA-A antigens

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(c) Irradiation

- Donor cells
  - Allele A
  - Allele B

Recipient cells lacking class II MHC of donor

Recipient cells sharing class II MHC of donor

Activation and proliferation of recipient cells

[3H]thymidine

Incorporation of radioactivity into cell nuclear DNA

No reaction
Uses of HLA typing

• For determination of HLA compatibility prior to transplantation
• For paternity testing
• For anthropologic studies
• For establishing HLA disease association
HLA and Disease

• Characteristics of HLA associated diseases:
  - unknown cause
  - unknown pathophysiologic mechanism with hereditary pattern of distribution
  - associated with immunologic abnormalities

• Graves disease: HLA-D or DR alleles
• Ankylosing spondylitis: HLA-B27
• Rheumatoid arthritis: HLA-DR4
• Iron storage disease and haemochromatosis: HLA-A3
General immunosuppressive therapy

- Non specific immunosuppression
- Risk of infections and lymphoid cancers
- Long term immunosuppression-increased risk of hypertension and metabolic bone disease
- Options:
  1. Mitotic inhibitors: Azathioprine, cyclophosphamide, methotrexate
  2. Corticosteroids: Prednisone, dexamethasone
  3. Immunosuppressants: Rapamycin and Cyclosporin A
  4. Irradiation of recipient’s lymphocytes
## Immunosuppressive agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Possible mode of action</th>
<th>Application(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Corticosteroids, prednisone</td>
<td>anti-inflammatory, altering T-cell and PMN traffic</td>
<td>organ transplant, hypersensitivity, autoimmune diseases</td>
</tr>
<tr>
<td>Cyclosporin, FK506</td>
<td>inhibition of IL-2 synthesis</td>
<td>organ transplant</td>
</tr>
<tr>
<td>Rapamycin</td>
<td>blocking of IL2-IL2R signal</td>
<td>organ transplant</td>
</tr>
<tr>
<td>Azathioprine, 6-MP</td>
<td>purine metabolism</td>
<td>organ transplant, autoimmune</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>folate metabolism</td>
<td>organ transplant, autoimmune</td>
</tr>
<tr>
<td>Cyclophosphamide, Melphalan</td>
<td>alkylation of DNA, RNA and proteins</td>
<td>organ transplant, autoimmune</td>
</tr>
</tbody>
</table>
Specific Immunosuppressive therapy

- Includes antigen specific immunosuppressant's that reduce immune response to alloantigen of the graft while preserving the recipient’s ability to respond to other foreign antigens

  1. Antibodies suppressing graft rejection
  2. Blocking costimulatory signals
Antibodies suppressing graft rejection

- Antithymocyte globulin
- Monoclonal antibody to CD3 molecule, CD25, CD20, CD4*, cell adhesion molecules, implicated cytokines
- Diphtheria toxin coupled with antibody
Blocking costimulatory signals

T cells that recognize graft antigens become activated
Graft rejected

T cells that recognize graft antigens lack co-stimulation and become anergic
Graft survives
Immune Tolerance to allografts

• Allograft may be accepted without the use of immunosuppressive therapy when:
  1. Tissue is lacking alloantigens e.g. cartilage and heart valves
  2. Tissue or cells are grafted to a privileged sites
  3. A state of tolerance has been induced biologically during perinatal exposure
Graft Versus Host Reaction

- Reverse of normal transplantation reaction,
- when immunologically competent cells of graft react against antigens of the host.
- Attributed to discrepancy in minor histocompatibility antigens.
- Following conditions are necessary for the development of GVH:
  1. Graft contains immunocompetent cells
  2. Recipient possesses transplantation antigens that are absent in the graft
  3. Recipient must not reject the graft
Pathogenesis of GVHD

CD4 and CD8 T cells of donor

Recognizes MHC (HLA) antigen of recipient as foreign

Attacks host tissue whose immune system is crippled (primary disease or myeloablation by cytotoxic drugs or irradiation)

Destruction of host tissue
GVHD
<table>
<thead>
<tr>
<th></th>
<th><strong>Acute GVHD</strong></th>
<th><strong>Chronic GVHD</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reaction time</strong></td>
<td>Days to weeks</td>
<td>After 100 days or more</td>
</tr>
<tr>
<td><strong>Skin involvement</strong></td>
<td>Generalized skin rash, desquamation in severe cases</td>
<td>Extensive cutaneous injury with destruction of skin appendages and fibrosis of the dermis</td>
</tr>
<tr>
<td><strong>Liver involvement</strong></td>
<td>Destruction of bile ducts → jaundice</td>
<td>Chronic liver disease → cholestatic jaundice</td>
</tr>
<tr>
<td><strong>GIT involvement</strong></td>
<td>Mucosal ulcerations → bloody diarrhea</td>
<td>Damage to GI mucosa → esophageal strictures</td>
</tr>
<tr>
<td><strong>Immune response</strong></td>
<td>Direct cytotoxicity by CD8 cells and cytokines by sensitised donor cells</td>
<td>Immune system is devastated with involution of thymus &amp; depletion of lymphocytes in lymph nodes</td>
</tr>
<tr>
<td><strong>Predisposition</strong></td>
<td>Various infections</td>
<td>Life threatening infections and autoimmune diseases</td>
</tr>
</tbody>
</table>

*Acute GVHD (Graft-versus-Host Disease):* A condition that occurs when the donor immune cells recognize the recipient's tissue as foreign and attack it.

*Chronic GVHD:* A prolonged immune response that occurs after a stem cell transplant or organ transplant. It is more common in patients who have undergone a stem cell transplant.
# Clinical Staging of GVHD

<table>
<thead>
<tr>
<th>Stage</th>
<th>Skin</th>
<th>Liver</th>
<th>GIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Maculopapular rash &lt;25% body surface</td>
<td>Serum bilirubin 2-3 mg/dl</td>
<td>&gt; 500 ml diarrhea/day</td>
</tr>
<tr>
<td>2</td>
<td>Maculopapular rash 25-50% body surface</td>
<td>Serum bilirubin 3-6 mg/dl</td>
<td>&gt;1000 ml diarrhea/day</td>
</tr>
<tr>
<td>3</td>
<td>Generalized erythroderma</td>
<td>Serum bilirubin 6-15 mg/dl</td>
<td>&gt;1500 ml diarrhea/day</td>
</tr>
<tr>
<td>4</td>
<td>Generalized erythroderma with bullous formation and desquamation</td>
<td>Serum bilirubin &gt; 15 mg/dl</td>
<td>Severe abdominal pain with or without ileus</td>
</tr>
</tbody>
</table>
Graft Versus Host Reaction

• **Prognosis:** Mortality high in untreated GVHD
  Severe GVHD - 70%
  Mild GVHD - 30%

• **Prevention:** Depletion of donor T cells before transplantation but incidence of graft failure and recurrence of diseases in leukemic patients increases

• **Treatment:** Increased immunosuppressive T/t but once GVHD has occurred, it is difficult to eradicate.
Fetus as allograft

- Fetus - mixture of maternal and paternal genes

- Fetal MHC antigens are always different from mother, still baby is not rejected because of immunosuppressive factors produced by fetus, placenta and mother
Fetus as allograft

1. Placental mucoproteins coating fetal cells
2. Soluble inhibitory factor produced by placental giant cells
3. Hormones- HCG, High levels of maternal, progesterone
4. Blocking antibodies to fetal antigens
5. α fetoprotein
6. β₁ glycoprotein of fetal origin
   - Fetus depress immune response of mother, but can’t reject the mother because of immature immune system
Clinical transplantation

• For a number of illnesses, a transplant is the only means of therapy.
• Routinely done transplantations are: kidney, liver, heart, lung, bone marrow, blood pancreas, skin, cornea etc.
• Combination of organs are also being done with increasing frequency
**Cornea**
- From cadaver
- Immunosuppression not required
- 40,000 transplants per year

**Lung**
- From brain-dead donor
- Procedure recently developed
- Little data available
- 955 transplants in 2000
- Often heart/lung transplant (47 in 2000)

**Heart**
- From brain-dead donor
- HLA matching useful but often impossible
- Risk of coronary artery damage, perhaps mediated by host antibody
- 2172 transplants in 2000

**Liver**
- From cadaver
- Surgical implantation complex
- Resistant to hyperacute rejection
- Risk of GVHD
- 4816 transplants in 2000

**Bone marrow**
- Needle aspiration from living donor
- Implanted by IV injection
- Risk of GVHD very low
- 13,258 transplants in 2000

**Kidney**
- From live donor or cadaver
- ABO and HLA matching required
- Rejection rare but GVHD a risk

**Skin**
- Mostly autologous (burn victims)
- Temporary grafts of nonviable tissue
- Allogeneic grafts rare, require immunosuppression

**Blood**
- Transfused from living donor
- ABO and Rh matching required
- Complications extremely rare
- An estimated 14 million units used each year

**Pancreas**
- From cadaver
- Islet cells from organ sufficient
- 420 transplants in 2000
- Increasingly, pancreas/kidney transplant for advanced diabetes (910 in 2000)
Xenotransplantation

• For human transplantation of organs, usually live donors and cadavers are the source. But the supply is insufficient to meet the demands of thousands of patients waiting for the transplant.

• To meet the shortfall, various potential animal donors can be utilized.
Xenotransplantation

- Primates e.g., Chimpanzees, Baboons - closely related to humans but the availability of large primates will be extremely limited.

- Pigs - breed rapidly and have large litters. Can be housed in pathogen free environment and share considerable anatomic and physiologic similarity.
Transplantation-Indian Scenario

• Transplantation of Human Organs Act (1994) laid down the provisions for transplantation in India.

• Today there are many centers in India performing organ transplantation, but still the problem of illegal organ trafficking is an hindrance.
Transplantation-Indian Scenario

- First successful live Donor renal transplant done in CMC Vellore in Jan 1971

- First successful heart transplant in India is done in AIIMS by Dr. Venugopal in 1994

- First successful liver transplantation- 1998

- First successful combined renal and pancreatic transplantation done in 2005
Objectives of the National Transplant Registry

• The purpose of National Transplant Registry is to collect transplant related data from various centres in the country and to be able to collate the data from time to time to derive the following information:

  • The number of transplants done in the country.

  • Essential demographic data of Indian Patients undergoing transplants.

  • The immunosuppressive regimes used by various centres.

  • Short term and long term results of the allograft.
• Complications during management in short term and long term.

• Patient survival after transplants.

• The HLA profile of Indian Patients.

• Number of Living and cadaver transplants.

• Relationship in case of related transplants.

• Profile of Donors
Transplantation-Indian Scenario

Total Renal Transplant Data (1971 - 2009): 18,121
Data from Hospitals : 33
Cancer immunology
Cancer

- Cancer cells can be viewed as altered self cells that have escaped normal growth regulating mechanisms
Loss of Normal Growth Control

Normal cell division

Cell damage—no repair

Cell Suicide or Apoptosis

Cancer cell division

First mutation  Second mutation  Third mutation  Fourth or later mutation

Uncontrolled growth
Cancer immunology

- It is the study of
  - The antigenic properties of transformed cells
  - The host immune response to these tumor cells
  - The immunological consequences to the host of the growth of malignant cells
  - The means by which the immune system can be modulated to recognize tumor cells and promote tumor eradication
Etiology

- Inherited - expression of inherited oncogene e.g. viral gene incorporated into host gene
- Viral - HPV, HHV-8, HBV, EBV (DNA)
  - Human T-cell leukemia virus (RNA)
- Bacterial - Helicobacter pylori
- Parasites - Schistosoma haematobium,
- Chemical - Polycyclic hydrocarbons, Formaldehyde
  - Aromatic amines, Coal tar, Arsenic
  - Alkyl nitroso amines, Nicotine, Carbaryl
- Radiological - Ultraviolet & Ionising radiation
- Spontaneous
Cell Growth

Control of cell growth

Growth promoting Proto-oncogenes

Growth restricting Tumor suppressor genes
Molecular Basis of Cancer

Conversion of proto-oncogenes to oncogenes:
• Amplification of c-erbB2 in breast cancer
• Point mutation of c-ras in kidney and bladder cancers
• Chromosome translocation of c-myc in Burkitt’s lymphoma

Altered tumor-suppressor genes:
• P53 mutation in prostate cancer: failure in cell cycle arrest or apoptosis of prostate tumors

Uncontrolled cell growth
Tumor suppressor gene

• *Cancer associated gene or anti oncogene*
• *It encodes the protein that inhibit excessive cell proliferation*
• *Inactivation of these genes results in unregulated proliferation.*
<table>
<thead>
<tr>
<th>Name/type</th>
<th>Category 11: Tumor suppressor gene, inhibitors of cellular proliferation</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Rb$</td>
<td>Suppressor of retinoblastoma</td>
</tr>
<tr>
<td>$P53$</td>
<td>Nuclear phosphoprotein that inhibit carcinoma of lung and colon</td>
</tr>
<tr>
<td>$DCC$</td>
<td>Suppressor of colon carcinoma</td>
</tr>
<tr>
<td>$APC$</td>
<td>Suppressor of adenomatous polyposis</td>
</tr>
<tr>
<td>$NF1$</td>
<td>Suppressor of neurofibromatosis</td>
</tr>
<tr>
<td>$WT1$</td>
<td>Suppressor of Wilm’s tumor</td>
</tr>
</tbody>
</table>
Tumor Antigens

- Study of antigens on tumor cells and the immune response to these antigens.
- Two types
  1. TSTAs- Tumor specific transplantation Ag
  2. TATAs- Tumor associated transplantation Ag
Tumor Antigens

- All belong to heat shock protein family.
- HSP molecules bind to APCs and target the peptides with high efficiency.
- The HSP molecules stimulate the APCs to mediate maturation of dendritic cells & secretion of an array of cytokines that help in adaptive response.
TSTA

• Unique to tumor cells & do not occur on normal cells.
• Mutations in tumor cells that generate altered cellular proteins
• Cytosolic processing of protein leads to peptides
• Peptides presented to class 1 MHC leads to cell mediated response by tumor specific CTLs
• Example- HPV - E7 antigen
Antigens expressed on tumor cells

Major Histocompatibility Complex antigens

**TSTA:** unique to a tumor
Play an important role in tumor rejection.

**TATA:** shared by normal and tumor cells
TATA

- Not unique to the tumor cells
- May be proteins that are expressed on normal cells during fetal development.
- It can be proteins that are expressed at extremely low levels on normal cells but are expressed at much higher level on tumor cells
- Reactivation of embryonic genes that lead to their expression on the fully differentiated tumor cells.
- Example- alphafetoprotein, CEA, Gp 100
Oncofetal tumor antigens

• Found on normal fetal cells
• Antigens appear in early embryonic development
• If these antigens appear later in life on cancer cells, they are recognized as non self & induce an immunological response

1) Alfa fetal protein (AFP)- liver carcinoma
2) Carcinoembryonic antigen (CEA)- colorectal carcinoma
Tumor markers

- **CEA** - colon carcinoma
- **α-fetoprotein** - liver carcinoma, yolk sac carcinoma
- **β-HCG** - Choriocarcinoma,
- Prostate specific antigen - Prostate carcinoma
- **CA 125** - Ovarian carcinoma
- **CA 15-3** - Breast carcinoma
- **CA 19-9** - Colon carcinoma

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Immune response

- Both humoral and cell mediated response
- Cell mediated response plays the major role
- Natural killer cells
- Macrophages

✓ Immune Surveillance- Immune response recognize the nascent transformed cell & destroy it.
Secretion of IFN-\(\gamma\), TNF-\(\alpha\) and Nitric Oxide by Innate immune cells

NATURAL KILLER (NK) CELL

Lysis of glioma cell

MICA/B

NEUTROPHIL

Nitric oxide

MACROPHAGE / MICROGLIA

Tumor cell debris (i.e. HSP-tumor antigen complexes) are phagocytosed and then presented with MHC by APC's

Tumor antigens are presented to T cells in the context of MHC class I and II.

DENDRITIC CELL

MHC Class II

MHC Class I

NKG2D

IFN-\(\gamma\)
Cellular mechanisms in tumor immunity

- T cells - plays role in control of growth
  - MHC class I restricted cytotoxic T cells
  - MHC class II restricted helper T cells
  - MHC class I helper T cells cannot directly recognize tumor cells
  - Helper T cells dependent upon APC such as macrophages, to present tumor antigens in association with MHC class II antigens
  - It leads to T helper cell activated & subsequent IL-2 secretion.
  - It activates cytotoxic T cells, macrophages, NK cells & B cells.
Cellular mechanisms

- T helper cells also secrete lymphotoxin and tumor necrosis factor which directly lyse the tumor cells.
- The activated cytotoxic T cells recognize tumor targets and cause direct cell-mediated cytotoxicity.
Tumor evasion of the immune system

- Rapid growth (weak immunogenicity)
- Modulation of tumor antigens
- Masking of tumor antigens
- Induction of immune tolerance (expression of immune suppressants- IL-10, TGF-β)
- Antitumor antibodies can enhance tumor growth
- Production of blocking antibodies
- Expression of low level of class 1 MHC molecules
- Poor costimulatory signals
Antitumor Ab

• Ab bound to tumor specific Ag mask the Ag from cytotoxic T cells
• Ab with tumor Ag block CTL response
• Immune complex may inhibit ADCC by binding to Fc receptors on natural killer cells or macrophages & blocking their activity
Cancer immunotherapy

- Antigen nonspecific -
  - BCG vaccine
  - *Corynebacterium parvum*
- Antigen specific -
  - Vaccination with tumor antigens
  - Immune RNA, Transfer factor
  - Monoclonal antibodies
Cancer immunotherapy

- Manipulation of costimulatory signals can enhance immunity
- Enhancement of APC activity can modulate tumor immunity
- Cytokine therapy can augment immune responses to tumor
- Monoclonal antibodies are effective in treatment of some tumor
Cytokines licensed for human use

- **IL 2**
  - Advanced kidney cancer& for metastatic melanoma.

- **IFN α**
  - Hairy cell leukemia,
  - Chronic myelogenous leukemia
  - Cutaneous T cell lymphoma
  - Non-Hodgkin lymphoma
  - Solid tumor such as melanoma, RCC
<table>
<thead>
<tr>
<th>Monoclonal antibodies</th>
<th>Used to treat</th>
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</thead>
<tbody>
<tr>
<td>Rituximab</td>
<td>Non-Hodgkin’s Lymphoma</td>
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<tr>
<td>Trastuzumab</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Gemtuzumab ozogamicin</td>
<td>Acute myelogenous leukemia</td>
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<tr>
<td>Alemtuzumab</td>
<td>Chronic lymphocytic leukemia</td>
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<tr>
<td>Ibritumomab tiuxetan</td>
<td>Non Hodgkin’s lymphoma</td>
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<tr>
<td>Tositumomab</td>
<td>Non Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>Colorectal cancer, Head and neck cancer</td>
</tr>
</tbody>
</table>
Cancer vaccines

- Vaccine against cervical cancer-
  - Preventing cervical cancer against HPV infection
  - Viral proteins L1 or L2 from the cancer causing serotype provide prophylactic vaccine.
  - L1 when expressed in transfected cell lines-it assemble into particle – VLP
  - Two candidates on clinical trails-
    1. VLP composed of L1 of HPV serotype 6,11,16,18 with alum as adjuvant
    2. VLP composed of L1 of HPV serotype 16,18 with adjuvant ASO4 (alum with bacterial lipid)
HPV vaccine

• Age- 9-26 yrs
• Three doses-
  • Dose 1== when your doctor advise
  • Dose 2== 2 month after first dose
  • Dose 3== 6 month after first dose
• Cost – around Rs 3200/-
Other vaccines

- Cervical cancer
- Prostate cancer
- Kidney cancer
- Breast cancer