IMMUNOLOGY OF TRANSPLANTATION

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Introduction

- Transplantation immunology – sequence of events that occurs after an allograft or xenograft is removed from donor and then transplanted into a recipient.

- A major limitation to the success of transplantation is the immune response of the recipient to the donor tissue.
Transplant immunology

- As early as first half of last century, principle of graft failure thought to be
  - graft rejection is donor specific
  - Rejection possesses memory
  - First sit rejection is cell mediated
  - Second sit rejection is largely antibodies mediated
Tissue typing

- Can determined the chance of success
- Class 1 can be defined by
  - Monoclonal antibodies
  - Flow cytometry
  - Polymerized chain reaction (PCR)
- Class 1 are expressed on all nucleated cells
- Class 2 used to identified by Mixed leucocytes reaction
- Class 2 are expressed on B–Lymphocyte, Monocyte, Macrophages, Breast epithelia and respiratory epithelia
T- lymphocyte

- Lymphocyte with thymus maturation
- Carries specific cell receptors and marker
- They can recognize foreign antigen presented by APC (antigen presenting cell)
- Once presented with an antigen they will produce IL, and other factors, proliferate (cloning)
The best is by induction of tolerance
Radiation
Chemo reduction
Immunology of Transplant Rejection

Components of the Immune system involved in graft Rejection:

1) Antigen presenting cells –
   - Dendritic cells
   - Macrophages
   - Activated B Cells

2) B cells and antibodies –
   - Preformed antibodies
   - Natural antibodies
   - Preformed antibodies from prior sensitization
   - Induced antibodies

3) T cells

4) Other cells –
   - Natural killer cells
   - T cells that express NK cell – associated Markers
   - Monocytes/Macrophages
Transplant immunity

“Laws” of transplantation:

- Autogeneic grafts survive
- Syngeneic grafts survive
- Allogeneic grafts are rejected
- Parent-to-F1 grafts survive
- F1-to-parent grafts are rejected
- Xenogeneic grafts are rejected

In an allogeneic graft, donor and recipient cells should have very similar types of surface antigens.

So, why are allogeneic grafts always rejected?
Transplantation antigens

- Major histocompatibility antigens (MHC molecules)
- Minor histocompatibility antigens
- Other alloantigens
Immune system distinguishes self from non-self

Antigen: anything that can trigger an immune response

B-cell (lymphocyte) – secretes antibodies, presents antigen to T-cell

T-cell (lymphocyte), secretes cytokines (ex. IL-2), directs and regulates immune responses, also attacks infected, cancerous or foreign cells
Cytokines are chemical messengers – bind to target cells, encourage cell growth, trigger cell activity, direct cell traffic, destroy target cells, and activate phagocytes (“cell eaters”)

IL-2 activates T-cells and causes proliferation

T-cell surface markers (CD3, CD25, CD52 and T-cell receptor) CD=cluster of differentiation of T-cells
MAJOR HISTOCOMPATIBILITY COMPLEX (MHC)

- Is located on short arm of chromosome 6
- It includes 3 regions: class Ia (loci A, B, C) class Ib (loci E, F, G, H), class II (loci DR, DQ, DP) and class III
- Genes of class Ia and class II are highly polymorphic, while those of class Ib and class III are not
- Polymorphism means occurrence of several alleles ie. genes encoding various MHC antigens located at the same locus
MAJOR HISTOCOMPATIBILITY ANTIGENS

- Histocompatibility antigens are cell surface expressed on all cells (class I) and on APC, B cells, monocytes/macrophages (class II)
- They are targets for rejection
- They are inherited from both parents as MHC haplotypes and are co-dominantly expressed
They also participate in rejection but to lesser degree

Disparity of several minor antigens may result in rejection, even when MHC antigens are concordant between donor and recipient

They include blood group antigens, tissue and organ antigens, normal cellular constituents

They are peptides derived from polymorphic cellular proteins bound to MHC class I molecules
MHC Complex

- Are carried on short arm of chromosome 6
- Classified in Class 1, class 2 and class 3
- Class 1 of HLA-A, HLA-B and HLA-C
- Class 2 of HLA-DR groups
- Class 3 are many factors including complement and INF

- Class I HLA A, B, C bind to TCR on CD8 T-Cell
- Class II DR, DP, DQ bind to TCR on CD4 T-Cell
- Most polymorphic genes in human genome
- Co-dominantly expressed
Tolerance

- Tolerance—\(\rightarrow\) specific unresponsiveness triggered by previous exposure to Ag.

- **Natural Tolerance (self tolerance):** Unresponsiveness to self Ags.

- **Acquired tolerance:** Unresponsiveness to foreign Ags.
Why is it important to study tolerance?

- Autoimmunity
- Cancer
- Transplantation
- Infections
- Vaccines
TYPES OF GRAFTS

- **Autologous graft (autograft)** – in the same individual: from one site to another one
- **Isogenic (isograft)** – between genetically identical individuals
- **Allogeneic (allograft or homograft)** – between different members of the same species
- **Xenogeneic (xenograft)** – between members of different species
Autograft
Within an individual

Isograft
Identical Twins

Allograft
Non-identical

Xenograft
Between species
Today it is possible to transplant many different organs and tissues including.

- Most common transplantation is blood transfusion.
- Bone Marrow transplantation
- Organs: Heart, kidneys, pancreas, lungs, liver and intestines.
- Tissues: include bones, corneas, skin, heart valves, veins, cartilage and other connective tissues.
# Most Common Transplantation

## Blood Transfusion

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- Green: Transfuse
- Red: Not transfused
What led to recognition of donor tissue as foreign?
The response to transplanted tissue is genetically determined
Transferred tissue carries antigens
Immune response well be evoked
HLA (Human Leukocyte associated antigens) are the major determinant of histo-compatibility MHC
MHC Complex are specialized cell surface molecules
MECHANISMS OF REJECTION
MECHANISMS OF REJECTION

- Depend on disparity of genetic background between donor and recipient
- T cells are critical in graft rejection
- Rejection responses in molecular terms, are due to TCR–MHC interaction
- Graft and host MHC molecules present different peptides
- Different MHC molecules have different peptide-binding grooves
- T lymphocytes can directly recognize and respond to foreign MHC molecules
ALLOREACTIVE CELLS ARE SO COMMON, BECAUSE:

- Foreign MHC molecules differ from self MHC at multiple different aminoacid residues, each of which may produce determinant recognized by a different cross-reactive T cell clone
- Thus, each foreign MHC molecule is recognized by multiple clones of T cells
- 2% of host T cells are capable recognizing and responding to a single MHC foreign molecule
Recognition of Alloantigens

- **Direct Presentation (donor APC)**
  - Recognition of an intact MHC molecule displayed by donor APC in the graft
  - Basically, self MHC molecule recognizes the structure of an intact allogeneic MHC molecule
  - Involves both CD8+ and CD4+ T cells.
Indirect Presentation (Host APC)

- Donor MHC is processed and presented by recipient APC
- Basically, donor MHC molecule is handled like any other foreign antigen
- Involve only CD4+ T cells.
- Antigen presentation by class II MHC molecules
Direct allore cognition

Donor dendritic cell

Donor MHC + peptide

Recipient CD4+ T cell

Predominant role in acute rejection

Indirect allore cognition

Recipient dendritic cell

Uptake

Processing

Recipient MHC + allopeptide derived from processed donor MHC

Provides B-cell help for alloantibody production
Important in chronic graft damage
Suggested in activation of Tregs
### Difference between Direct Recognition and Indirect Recognition

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<td><strong>Intact allogeneic MHC molecule</strong></td>
<td><strong>Peptide of allogeneic MHC molecule</strong></td>
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<td><strong>APCs</strong></td>
<td><strong>Recipient APCs are not necessary</strong></td>
<td><strong>Recipient APCs</strong></td>
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<tr>
<td><strong>Activated T cells</strong></td>
<td><strong>CD4 + T cells and/or CD8 + T cells</strong></td>
<td><strong>CD4 + T cells and/or CD8 + T cells</strong></td>
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<td><strong>Roles in rejection</strong></td>
<td><strong>Acute rejection</strong></td>
<td><strong>Chronic rejection</strong></td>
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<td><strong>Degree of rejection</strong></td>
<td><strong>Vigorous</strong></td>
<td><strong>Weak</strong></td>
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The Immunology of Allogeneic Transplantation

- Recognition of transplanted cells that are self or foreign is determined by polymorphic genes (MHC) that are inherited from both parents and are expressed co-dominantly.

- Alloantigens elicit both cell-mediated and humoral immune responses.
Donor APCs migrate to regional lymph nodes and are recognized by the recipient’s $T_H$ cells. Alloreactive $T_H$ cells in the recipient induce generation of $T_{DTH}$ cell and CTLs then migrate into the graft and cause graft rejection.
Activation of Alloreactive T cells and Rejection of Allografts

(SENSATIZATION)

Donor kidney

Passenger leukocyte

Class II MHC. antigen

CTL

TDM

EFFECOR

LYMPH NODE

Tn

Tn

Tn

IL-2

Tn

Tn

Tn

Tn

Tn
Donor APC

Class II

Class I

CD4+ Helper Cell

Help

CD8+ pCTL

Sensitization

Donor Cells

Class I

CD8+ CTL

Effector
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Activation of Alloreactive T cells and Rejection of Allografts

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T_{DM}

EFFECTOR

LYMPH NODE

IL-2

T_{H}

T_{H}

T_{H}

T_{DM}

CTL

CTL
Classification of Allograft Rejection

- Host versus graft reaction (HVGR)
  - Conventional organ transplantation
- Graft versus host reaction (GVHR)
  - Bone marrow transplantation
  - Immune cells transplantation
Types OF REJECTION

- **Hyperacute rejection** (hours or first days) antibodies to HLA and ABO blood group system
  Preformed circulating cytotoxic antibodies

- **Acute rejection**
  Acute (days or weeks): 5–14 days
  Cell mediated (T cells)

- **Chronic rejection**
  various mechanisms: cell–mediated, deposition of antibodies or antigen antibody complexes with subsequent obliteration of blood vessels and interstitial fibrosis (months or years)
  Ischemic graft damage, micro vascular endothelial damage
Hyperacute Rejection

- Characterized by thrombotic occlusion of the graft
- Begins within minutes or hours after anastamosis
- Pre-existing antibodies in the host circulation bind to donor endothelial antigens
- Activates Complement Cascade
- Xenograft Response
Hyperacute Rejection

1. Preformed Ab, 2. complement activation, 3. neutrophil margination, 4. inflammation, 5. Thrombosis formation
Acute Rejection

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

1. T-cell, macrophage and Ab mediated,
2. myocyte and endothelial damage,
3. Inflammation
Chronic Rejection

- Occurs in most solid organ transplants
  - Heart
  - Kidney
  - Lung
  - Liver

- Characterized by fibrosis and vascular abnormalities with loss of graft function over a prolonged period.
Chronic Rejection

1. Macrophage – T cell mediated
2. Concentric medial hyperplasia
3. Chronic DTH reaction
Is the result of organ damage by immunologic and non-immunologic factors

Initially – the minor damage and activation of endothelium by cytotoxic T cells and antibodies
Production by endothelial cells biologically active mediators (PDGF, PAF, TNF, thromboxans etc.)

- Secretion of cytokines by infiltrating lymphocytes

- Mitogenic effect on myocytes and fibroblasts results in cell proliferation and fibrosis
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

Capillary endothelial walls

Enzymes

Platelets
Figure 16–6  Histopathology of different forms of graft rejection.

A. Hyperacute rejection of a kidney allograft with endothelial damage, platelet and thrombin thrombi, and early neutrophil infiltration in a glomerulus.

B. Acute rejection of a kidney with inflammatory cells in the interstitium and between epithelial cells of the tubules.

C. Acute rejection of a kidney allograft with destructive inflammatory reaction destroying the endothelial layer of an artery.

D. Chronic rejection in a kidney allograft with graft arteriosclerosis. The vascular lumen is replaced by an accumulation of smooth muscle cells and connective tissue in the vessel intima. (Courtesy of Dr. Helmut Rennke, Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston.)
VARIABLES DETERMINING TRANSPLANT OUTCOME

- Donor–host antigenic disparity
- Strength of host anti donor response
- Immunosuppressive regimen
- The condition of the allograft
- Primary disease of the host
CHRONIC REJECTION IS MORE FREQUENT WHEN:

- Were previous episodes of acute rejection
- There is a low number of compatible HLA antigens with recipient
- Patient on inadequate immunosuppression
In the case of cytomegaly virus infection
The period of organ storage was too long
Patient is heavy smoker and/or is hyperlipidemic
Organ mass is unproportionally small as compared to body mass
GRAFT VERSUS HOST DISEASE (GVHD)
Graft versus host reaction (GVHR)

- Graft versus host reaction (GVHR)
  - Allogeneic bone marrow transplantation
  - Rejection to host alloantigens
  - Mediated by immune competent cells in bone marrow

Graft versus host disease (GVHD)

- Graft versus host disease (GVHD)
  - A disease caused by GVHR, which can damage the host
  - Is common complication in recipients of bone marrow transplants
Graft vs. Host Disease

- Caused by the reaction of grafted mature T-cells in the marrow inoculum with alloantigens of the host
- **Acute GVHD**
  - Characterized by epithelial cell death in the skin, GI tract, and liver
- **Chronic GVHD**
  - Characterized by atrophy and fibrosis of one or more of these same target organs as well as the lungs
Graft versus host disease
Graft versus host disease
Acute graft-versus-host reaction with vivid palmar erythema
Early, chronic graft-versus-host reaction with widespread, almost confluent hyperpigmented lichenoid papules and toxic epidermal necrosis-like appearance on knee.

Late, chronic graft-versus-host reaction with hyperpigmented sclerotic plaques on the back.
GRAFT VERSUS HOST DISEASE (GVH)

- It may be avoided by careful typing, removal of mature T cells from the graft and by immunosuppressive drugs.

- It is manifested by marked rise of several cytokines in patient’s serum (IFN-γ, TNF, IL-1, IL-2, IL-4).
RISK FACTORS IN FORMATION OF GVH

**Acute GVH**
- Previous pregnancies in female donor
- High T cell number in marrow
- HLA disparity
- Transplant from female to male
- Low immunosuppression
- Herpes virus infection

**Chronic GVH**
- Aging of donor and recipient
- Donor’s leukocyte transfusion
- Previous acute GVH
- High dosage radiation
- Transplant from female to man
- HLA disparity
thanks
Xenogeneic transplantation
Potential advantage due to larger accessibility of animal organs

Monkeys are apparently the most suitable donors, but dangerous because of potential risk of retrovirus transfer within graft
Pigs are now considered because of similar sizes of organs and erythrocytes to human ones.

The major obstacle – presence in man (1%) of natural antibodies vs. Gal (galactose-\(\alpha\)-1,3-galactose) causing hyperacute rejection.
Xenogenic Transplantation

- >50,000 people that need organs die while waiting for a donor
- Studies are underway involving nonhuman organs
- Attention has been focused on the pig but the problem is the existence of natural or preformed antibodies to carbohydrate moieties expressed in the grafts endothelial cells
- As a consequence activation of the compliment cascade occurs rapidly and hyperacute rejection ensues
- Concern has given to debate about the safe use of xenografts and animal tissues that the tissues might harbor germs
stem cells for Transplants
Source of stem cells for Transplants

- Bone Marrow graft
- Peripheral Blood Stem Cells (PBSCT)
- Umbilical cord
Bone Marrow Transplantation

- Used for Leukemia, Anemia and immunodeficiency, especially severe combined immunodeficiency (SCID).
- About $10^9$ cells per kilogram of host body weight, is injected intravenously into the recipients.
- Recipient of a bone marrow transplant is immunologically suppressed before grafting.
- Eg. Leukemia patients are often treated with cyclophosphamide and total body irradiation to kill all cancerous cells.
- Because the donor bone marrow contains immunocompetent cells, the graft may reject the host, causing graft versus host disease (GVHD).
Peripheral Blood Stem Cells (PBSCT)

- Stem cells collected peripherally using apheresis (cell separator machine)
  - Less invasive; less discomfort; less morbidity than BM
- Outpatient procedure
- PBSCT results in more rapid hematopoietic recovery than BM
- No difference in treatment outcome
- Quickly replacing traditional BM

- Using cytokine stimulation (G–CSF injections)
- BM releases large number CD34 stem cells into circulation
  - Stem cells harvested via peripheral line
Goals of Transplant Research

- Prevent rejection and graft loss
- Reduce the amount of immunosuppression
  - Decrease side effects
  - Decrease toxicity and long term effects
- Enhance long term patient and graft survival
- Provide reasonable cost effective therapy
- Improve patient adherence and quality of life
- Induce Tolerance (no long term medications, reduces adverse effects, improves quality of life)
Immunosuppressive Agents
Management of a Transplant Recipient

- **Induction Therapy**: administer medications that provide marked suppression prior to and during the first week post transplantation, some agents can also block B–cell mediated rejection.

- **Maintenance Therapy**: administer immunosuppressive agents continuously to prevent acute rejection.

- Administer medications to induce Tolerance?
History of Kidney Transplantation

1950’s
- First successful kidney transplant
- Total body irradiation for immunosuppression
- Steroids

1960’s
- Azathioprine

1970’s
- Polyclonal antibodies – anti-lymphocyte globulin (now Atgam®, Thymoglobulin®)

1980’s
- Cyclosporine (Sandimmune®), “triple drug therapy”
- Monoclonal antibody, OKT3 (Orthoclone®) in 1985
Immunosuppressant Discoveries 1990–2000

Tacrolimus (Prograf®)
Mycophenolate Mofetil (Cellcept ®)
Basiliximab (Simulect ®)
Cyclosporine Microemulsion (Neoral ®)
Daclizumab (Zenapax ®)
Rabbit Antithymocyte globulin (Thymoglobin ®)
Sirolimus (Rapamune ®)
Cyclosporin (CsA), Tacrolimus (FK-506) – inhibit IL-2 production by T cells calcineurin antagonist

Sirolimus (rapamycin) – inhibits signals transmitted by IL-2 binding to IL-2R (antiproliferating effect)

Azathioprine – reduces numbers and function both, T and B cells, by inhibition of purine metabolism
Mycophenolate mofetil (MMF) – inhibits DNA synthesis and protein glycosylation

Anti–IL–2 monoclonal antibodies

FTY 720 – dramatic effect on lymphocyte migration
## Structure of HLA Antigens

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What is Tolerance?

Immunologic unresponsiveness by the recipient to the graft in the absence of maintenance immunosuppression.
Self–nonself discrimination

Self

No response

Non-self or foreign

Strong response