Transplantation Immunology

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Types of Grafts

- Autologous (self)
  - e.g., BM, peripheral blood stem cells, skin, bone
- Syngeneic (identical twin)
- Allogeneic (another human except identical twin)
- Xenogeneic (one species to another)

Rejection

- First Set Rejection
  - Skin graft in mice 7-10 days
- Second Set Rejection
  - Skin graft in mice in 2-3 days

Mechanisms

- Foreign alloantigen recognition
- Memory lymphocytes (adaptive immunity)
- Can be adoptively transferred

MHC Restricted Allograft Rejection

First & Second Allograft Rejection

AlloAntigen Recognition

- Major Histocompatibility Complex (MHC)
  - 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

- Direct presentation (Donor APC)
  - Unprocessed allogeneic MHC

- Indirect presentation (Host APC)
  - Processed peptide of allogeneic MHC
Map of Human MHC

T-Cell Recognition of Peptide-MHC Complex

Direct and Indirect Alloantigen Recognition

Activation of Alloreactive T-Cells

- APC (DC, Macrophages, B-cells)
  Alloantigens with both CD8 T-cells and CD4 T-cells
- Co-stimulation (Immuneological Synapse)
  APC
  - MHC
  - T-cell Ag Receptor (TCR)
  - B.1 (CD8), B.7.2 (CD4)
  - CD8
  - CD40
  - LFA-3
  - ICAM-1
  - LFA-1
- APC cytokine release + stimulation of T-cells
  - IL-12
  - IL-18
- In vitro measurement: Mixed Lymphocyte Reaction (MLR)

T-Cell Anergy vs T-Cell Activation

- Antigen recognition: T-cell response
  - "Ready"
  - Activated APC
    - Increased presentation of alloantigen
    - Inflammation
  - Activated T-cell
    - Cytokine production
    - T-cell proliferation and differentiation
Antigen Recognition & Immunological Synapse

T-Cell Transcriptional Factor Activation

**Mixed Lymphocyte Reaction (MLR)**

- **Definition & Mechanism**
  - In vitro test of T-cell regulation of allogeneic MHC
  - Stimulators (donor-irradiated mononuclear cells)
  - Responders (recipient mononuclear cells)
  - Measure proliferative response of responders (tritiated thymidine incorporation)

- **Requirements**
  - Can be adoptively transferred
  - Require co-stimulation
  - Require MHC
  - Require Class I differences for CD8 T-cell response
  - Require Class II differences for CD4 T-cell response

**Pathological Mechanism of Rejection**

<table>
<thead>
<tr>
<th>Solid Organ</th>
<th>Bone Marrow/PBSC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hyperacute</strong></td>
<td>Not Applicable</td>
</tr>
<tr>
<td>Minutes to hours</td>
<td></td>
</tr>
<tr>
<td>Preexisting antibodies (IgG)</td>
<td></td>
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<tr>
<td>Intravascular thrombosis</td>
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<tr>
<td>HS of blood transfusion, transplantation or multiple pregnancies</td>
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<table>
<thead>
<tr>
<th><strong>Acute Rejection</strong></th>
<th>Primary Graft Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Few days to weeks</td>
<td>10-30 days</td>
</tr>
<tr>
<td>CD4+ CD8 T-Cells</td>
<td>Host NK Cells</td>
</tr>
<tr>
<td>Humoral antibody response</td>
<td>Lysis of donor stem cells</td>
</tr>
<tr>
<td>Parenchymal damage &amp; Inflammation</td>
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<table>
<thead>
<tr>
<th><strong>Chronic Rejection</strong></th>
<th>Secondary Graft Failure</th>
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</thead>
<tbody>
<tr>
<td>Chronic fibrosis</td>
<td>30 days – 6 months</td>
</tr>
<tr>
<td>Accelerated arteriosclerosis</td>
<td>Autologous T-Cells</td>
</tr>
<tr>
<td>6 months to yrs</td>
<td>CD4 + CD8</td>
</tr>
<tr>
<td>CD4+CD8 (Th2)</td>
<td>Lysis of donor stem cells</td>
</tr>
<tr>
<td>Macrophages</td>
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</tbody>
</table>

**Immune Mechanisms of Solid Organ Allograft Rejection**

- **Primary Graft Failure**
  - 10-30 days
  - Host NK Cells
  - Lysis of donor stem cells

- **Secondary Graft Failure**
  - 30 days – 6 months
  - Autologous T-Cells
  - CD4 + CD8
  - Lysis of donor stem cells
Hyperacute, Acute, Chronic Kidney Allograft Rejection

Hyperacute Acute Acute Chronic

Prevention & Treatment of Allograft Rejection

- ABO Compatible
  (Prevent hyperacute rejection in solid organs)
  (Prevent transfusion reaction in BM/PBSC)
- MHC allele closely matched
- Calcineurin inhibitors
  - Cyclosporine binds to Cyclophilin
  - Tacrolimus (FK506) binds to FK Binding Proteins (FKBP)
  - Calcineurin activates Nuclear Factor of Activated T-Cells (NFAT)
  - NFAT promotes expression of IL-2
- IMPDH Inhibitors (Inosine Monophosphate Dehydrogenase)
  - Mycophenolate Mofetil (MMF)
  - Inhibits guanine nucleotide synthesis
  - Active metabolite is Mycophenolic acid (MPA)

Prevention & Treatment of Allograft Rejection

- Inhibition of mTOR
  - Rapamycin binds to FKBP
  - Inhibits mTOR
  - Inhibits IL-2 signaling
- Antibodies to T-Cells
  - OKT3 (Anti-CD3)
  - Daclizumab (Anti-CD25)
  - Alemtuzamab (Anti-CD52)
  - ATG
    (Antithymocyte Globulin, Rabbit and Horse)
- Corticosteroids
  - Prednisone/Solumedrol
- Anti-inflammatory
  - Infliximab
    (Anti-TNF-α Antibody)

Incidence of Renal Allograft Survival in Influenced by HLA Matching

Immunological Tolerance

- Immunological specific recognition of self antigen by specific lymphocytes
- Central tolerance (Thymus-derivived)
  - Negative selection of autoreactive T-Cells
  - Regulation of T-Cell development
- Peripheral Tolerance
  - Clonal anergy
    (Inadequate co-stimulation)
  - Deletion
    (Activation-induced cell death)
  - Regulatory / Suppressor Cells
    (Inhibit T-Cell activation / proliferation)

Mechanism of T-Cell Activation vs Tolerance
Mechanism of Tissue Tolerance to Skin AlloGrafts

Central T-Cell Tolerance Mechanisms (Deletion and Regulatory T-Cells)

Mechanism of T-Cell Inactivation (CTLA-4/B7 Interaction)

Mechanism of T-Cell Inhibition (Regulatory T-Cells)

General Indications of Blood and Marrow Transplantation

- Dose intensity for malignant tumor (DI)
- Graft vs Tumor (GVT)
- Gene replacement
- Graft vs Autoimmune (GVHI)
- Gene therapy
- Marrow failure
## Specific Indications (Pediatric)

<table>
<thead>
<tr>
<th>Malignant</th>
<th>Non-Malignant</th>
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<tbody>
<tr>
<td>• Leukemia</td>
<td>Marrow Failure</td>
</tr>
<tr>
<td>• Solid Tumors</td>
<td>Metabolic Disorders</td>
</tr>
<tr>
<td>• Lymphomas</td>
<td>Hemoglobinopathy</td>
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<tr>
<td></td>
<td>Histioctic</td>
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<tr>
<td></td>
<td>Immunodeficiency</td>
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<tr>
<td></td>
<td>Autoimmune</td>
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## Conditioning Therapy

<table>
<thead>
<tr>
<th>Myeloablative – TBI Based</th>
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<tbody>
<tr>
<td>Myeloablative - Non TBI Based</td>
<td></td>
</tr>
<tr>
<td>Non-Myeloablative</td>
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## Engraftment

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<tr>
<th>• Myeloid</th>
<th>Absolute neutrophil count ≥ 500/mm³ x 2 days after nadir</th>
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</thead>
<tbody>
<tr>
<td>• Platelet</td>
<td>Platelets ≥ 20 k/mm³ x 7 days untransfused after nadir</td>
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### Chimerism (Allogeneic)

- Fluorescence in situ Hybridization (FISH) (Sex mismatch)
- VNTR (Molecular)

## Complications (Acute)

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<tr>
<th>• Graft failure (GF)</th>
<th>• Hemorrhagic cystitis</th>
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<tr>
<td>• Graft vs Host Disease (GVHD)</td>
<td>• Infections</td>
</tr>
<tr>
<td>• Mucositis</td>
<td>• Persistent and/or recurrent disease</td>
</tr>
<tr>
<td>• Veno-occlusive disease (VOD)</td>
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## Essential Components Required for GVHD

- Immuno-incompetent host
- Infusion of competent donor T-cells
- HLA disparity between host and donor
Graft vs Host Disease

- Hyperacute: Day 0 – 7
- Acute: Day 7 – 100
- Chronic: Day 100 ≥

Acute Graft vs Host Disease

- Dermal (Skin): Maculopapular
  - Palms / Soles
  - Pruritic ± Cheeks / Ears / Neck / Trunk
  - Necrosis / Bullae
- Hepatic: Hyperbilirubinemia
- Transaminemia
- Gastrointestinal: Diarrhea
  - Abdominal pain
  - Vomiting
  - Nausea

Risk Factors of GVHD

- HLA disparity: 6/6 > 5/6 > 4/6
- Allo stem cell source: MRD > UCB > UBM
- Donor Age
- Sex incompatibility
- CMV incompatibility
- Immune suppression

Common Prophylactic Immune Suppressants

- Methotrexate (MTX)
- Cyclosporine (CSP)
- Prednisone (PDN)
- Tacrolimus (FK506)
- Mycophenolate Mofetil (MMF)
- Anti Thymocyte Globulin (ATG)
- Alemtuzumab (Campath)
- T-Cell Depletion

Risk of Acute GVHD and HLA Disparity

Chronic GVHD

- Skin: Rash (lichenoid, scleroderma, hypopigmented, flaky), Alopecia
- Joints: Arthritis, arthropathy
- Oral/Ocular: Sjogren’s Syndrome
- Hepatic: Transaminemia, hyperbilirubinemia, cirrhosis
- GI: Dysphagia, pain, vomiting, diarrhea, abdominal pain
- Pulmonary: Bronchiolitis obliterans (BO), Bronchiolitis obliterans Organizing Pneumonia (BOOP)
- Hematologic/Immune: Cytopenias, dysfunction
- Serositis: Pericardial, pleural

Beatty et al NEJM: 313; 765, 1985
<table>
<thead>
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<th>Summary</th>
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<tr>
<td>• Transplantation grafts (Auto, Syn, Allo, Xeno)</td>
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<tr>
<td>• First &amp; second graft rejection</td>
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<tr>
<td>• MHC Class I &amp; II recognition</td>
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<tr>
<td>• Direct &amp; indirect MHC presentation</td>
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<tr>
<td>• APC T-cell activation</td>
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<td>• Mixed Lymphocyte Reaction (MLR)</td>
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<td>• Pathological mechanisms of rejection (Hyperacute, Acute, Chronic)</td>
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<td>• Prevention of rejection</td>
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<td>• Immunosuppressive medications</td>
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<tr>
<td>• Mechanisms of immune tolerance</td>
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<tr>
<td>• Diseases treatable by BMT</td>
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<tr>
<td>• Graft-versus-host (GVH) disease</td>
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