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 Anergy vs T-Cell Activation

T-Cell Recognition of Peptide-MHC Complex

Antigen Recognition & Immunological Synapse

Direct and Indirect AlloAntigen Recognition

Mixed Lymphocyte Reaction (MLR)

- Definition & Mechanism
  - In vitro test of T-cell regulation of allogeneic MHC
  - Stimulators (donor-modulated 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
Mixed Lymphocyte Reaction (MLR)

Pathological Mechanism of Rejection

<table>
<thead>
<tr>
<th>Solid Organ</th>
<th>Bone Marrow/PBSC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute</td>
<td>Not Applicable</td>
</tr>
<tr>
<td>- Minutes to hours</td>
<td></td>
</tr>
<tr>
<td>- Preexisting antibodies (IgG)</td>
<td></td>
</tr>
<tr>
<td>- Intravascular thrombosis</td>
<td></td>
</tr>
<tr>
<td>- History of blood transfusion, transplantation or multiple pregnancies</td>
<td></td>
</tr>
<tr>
<td>Acute Rejection</td>
<td></td>
</tr>
<tr>
<td>- Few days to weeks</td>
<td></td>
</tr>
<tr>
<td>- CD4+CD8 T-Cells</td>
<td></td>
</tr>
<tr>
<td>- Humoral antibody response</td>
<td></td>
</tr>
<tr>
<td>- Parenchymal damage &amp; Inflammation</td>
<td></td>
</tr>
<tr>
<td>Chronic Rejection</td>
<td></td>
</tr>
<tr>
<td>- Chronic fibrosis</td>
<td></td>
</tr>
<tr>
<td>- Accelerated arteriosclerosis</td>
<td></td>
</tr>
<tr>
<td>- 6 months to yrs</td>
<td></td>
</tr>
<tr>
<td>- CD4, CD8, (Th2)</td>
<td></td>
</tr>
<tr>
<td>- Macrophages</td>
<td></td>
</tr>
</tbody>
</table>

Hyperacute, Acute, Chronic Kidney Allograft Rejection

Mechanisms of Acute 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

Immune Mechanisms of Solid Organ Allograft Rejection

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)

- Corticosteroids
  - Prednisone/Solumedrol
  - Inhibits Macrophage Cytokine Secretion

- Anti-inflammatory
  - Infliximab (Anti-TNF-α Antibody)

- Block B7 Co-Stimulation
  - CTLA-4 Ig
  - Blocks T-Cell Activation
  - Induces Tolerance

- Block CD40 Ligand Binding
  - Anti CD40 Ligand
  - Inhibits Macrophage & Endothelial Activation

**Incidence of Renal Allograft Survival in Influenced by HLA Matching**

**Immunological Tolerance**

- Immunological specific recognition of self antigen by specific lymphocytes

- Central tolerance (Thymus-derivered)
  - 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)

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

**Mechanism of T-Cell Activation vs Tolerance**

**Mechanism of T-Cell Inactivation (CTLA-4/B7 Interaction)**
Mechanism of T-Cell Inhibition (Regulatory T-Cells)

Specific Indications (Pediatric)

Non-Malignant
- Marrow Failure
- Metabolic Disorders
- Hemoglobinopathy
- Histiocytic
- Immunodeficiency
- Autoimmune

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)

Malignant
- Leukemia
- Solid Tumors
- Lymphomas

Conditioning Therapy
- Myeloablative – TBI Based
- Myeloablative - Non TBI Based
- Non-Myeloablative

Engraftment
- Myeloid Absolute neutrophil count $\geq 500/mm^3 \times 2$ days after nadir
- Platelet Platelets $\geq 20 \times 10^3/mm^3 \times 7$ days untransfused after nadir

Chimerism (Allogeneic)
- Fluorescence in situ Hybridization (FISH) (Sex mismatch)
- VNTR (Molecular)
Complications (Acute)

- Graft failure (GF)
- Graft vs Host Disease (GVHD)
- Mucositis
- Veno-occlusive disease (VOD)
- Hemorrhagic cystitis
- Infections
- Persistent and/or recurrent disease

Essential Components Required for GVHD

- Immuno-incompetent host
- Infusion of competent donor T-cells
- HLA disparity between host and donor

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

Graft vs Host Disease

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

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

<table>
<thead>
<tr>
<th>Skin:</th>
<th>Rash (lichenoid, sclerodermatous, hyper/hypo pigmented, flaky), Alopecia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joints:</td>
<td>Arthralgia, arthritis, contractures</td>
</tr>
<tr>
<td>Oral/Ocular:</td>
<td>Sjogren's Syndrome</td>
</tr>
<tr>
<td>Hepatic:</td>
<td>Transaminemia, hyperbilirubinemia, cirrhosis</td>
</tr>
<tr>
<td>GI:</td>
<td>Dysphagia, pain, vomiting, diarrhea, abdominal pain</td>
</tr>
<tr>
<td>Pulmonary:</td>
<td>Bronchiolitis obliterans (BO), Bronchiolitis obliterans Organizing Pneumonia (BOOP)</td>
</tr>
<tr>
<td>Hematologic/Immune:</td>
<td>Cytopenias, dysfunction</td>
</tr>
<tr>
<td>Serositis:</td>
<td>Pericardial, pleural</td>
</tr>
</tbody>
</table>

Summary

- T-cell activation & proliferation requires immunological synapse with TCR/MHC and co-simulating ligands & receptors
- Tissue rejection may be hyperacute (preexisting Ab) acute (days to weeks) and/or chronic (months to years)
- Allogenic stem cell transplantation may result in hyperacute (1-7d), acute (7-10d) and/or chronic (100d – 5yr) GVHD.

Summary

- First set donor tissue rejection from a non-identical MHC recipient is a primary adaptive immune response
- Second set donor tissue rejection for a non-identical MHC recipient involves memory antigen host T & B cells
- Alloantigen antigen direct and indirect presentation involves donor and host APC, respectively