Transplantation Immunology

Mitchell S. Cairo, MD
Professor of Pediatrics, Medicine and Pathology
Chief, Division, Pediatric Hematology & Blood & Marrow Transplantation
Children’s Hospital New York Presbyterian
Tel – 212-305-8316
Fax – 212-305-8428
E-mail – mc1310@columbia.edu

Objectives

• Understand the immunological mechanisms responsible for first and second set allograft skin rejection
• Conceptualize direct and indirect alloantigen recognition
• Learn the definition and mechanism(s) associated with the mixed lymphocyte reaction (MLR)

Objectives

• Distinguish and compare the pathological mechanisms and description of hyperacute, acute and chronic solid organ vs. bone marrow allograft rejection
• Begin to understand the mechanisms of central and peripheral immunological tolerance
• Appreciate the general & specific indication for bone marrow transplantation and essential components for development of graft vs. host disease (GVHD)

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**

**Regulation of T-cell Activation and Tolerance by B7-CD28/CTLA-4 Pathway**

Sharpe et al., NEJM, 2006
Antigen Recognition & Immunological Synapse

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)
  - Measures 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>Hyperacute</td>
<td>Not Applicable</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Minutes to hours</td>
</tr>
<tr>
<td></td>
<td>Preexisting antibodies (IgG)</td>
</tr>
<tr>
<td></td>
<td>Intravascular thrombosis</td>
</tr>
<tr>
<td></td>
<td>Allo-HLA mismatch</td>
</tr>
<tr>
<td></td>
<td>Transplantation or multiple pregnancies</td>
</tr>
<tr>
<td>Acute Rejection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Few days to weeks</td>
</tr>
<tr>
<td></td>
<td>CD4 + CD8 T-Cells</td>
</tr>
<tr>
<td></td>
<td>Humoral antibody response</td>
</tr>
<tr>
<td></td>
<td>Parenchymal damage &amp; inflammation</td>
</tr>
<tr>
<td>Chronic Rejection</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chronic fibrosis</td>
</tr>
<tr>
<td></td>
<td>Accelerated atherosclerosis</td>
</tr>
<tr>
<td></td>
<td>6 months to yrs</td>
</tr>
<tr>
<td></td>
<td>CD4, CD8, (Th2)</td>
</tr>
<tr>
<td></td>
<td>Macrophages</td>
</tr>
<tr>
<td>Hyperacute, Acute, Chronic Kidney Allograft Reaction</td>
<td></td>
</tr>
</tbody>
</table>

Primary Graft Failure
- 0 – 14 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
Mechanisms of Acute 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
  - Daclizumab
- Corticosteroids
  - Prednisone/Solumedrol
  - Inhibits Macrophage Cytokine Secretion
  - Anti-inflammatory
  - Infliximab (Anti-TNF-α Antibody)
- Block B7 Co-Stimulation
  - CTLA-4 Ig
  - Inhibits T-cell activation
  - Induces Tolerance
  - Blocks B7 Co-Stimulation
- Block CD40 Ligand Binding
  - Anti-CD40 Ligand
  - Inhibits Macrophage & Endothelial Activation

Incidence of Renal Allograft Survival in Influenced by HLA Matching

- Prevention & Treatment of Allograft Rejection
- Mechanism of T-Cell Activation vs Tolerance
- Immunological Tolerance

- Immunological specific recognition of self antigen by specific lymphocytes
- Central tolerance (Thymus-derived)
  - 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 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)

Malignant

- Leukemia
- Solid Tumors
- Lymphomas

Conditioning Therapy

- Myeloablative – TBI Based
- Myeloablative - Non TBI Based
- Non-Myeloablative

Engraftment

- Myeloid: Absolute neutrophil count ≥ 500/mm³ x 2 days after nadir
- Platelet: Platelets ≥ 20 k/mm³ x 7 days untransfused after nadir

Chimerism (Allogeneic)

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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Graft failure (GF)</td>
</tr>
<tr>
<td>•</td>
<td>Graft vs Host Disease (GVHD)</td>
</tr>
<tr>
<td>•</td>
<td>Mucositis</td>
</tr>
<tr>
<td>•</td>
<td>Veno-occlusive disease (VOD)</td>
</tr>
</tbody>
</table>

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Hemorrhagic cystitis</td>
</tr>
<tr>
<td>•</td>
<td>Infections</td>
</tr>
<tr>
<td>•</td>
<td>Persistent and/or recurrent disease</td>
</tr>
</tbody>
</table>

## Essential Components Required for GVHD

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Immuno-incompetent host</td>
</tr>
<tr>
<td>•</td>
<td>Infusion of competent donor T-cells</td>
</tr>
<tr>
<td>•</td>
<td>HLA disparity between host and donor</td>
</tr>
</tbody>
</table>

## Graft vs Host Disease

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Hyperacute  Day 0 – 7</td>
</tr>
<tr>
<td>•</td>
<td>Acute  Day 7 – 100</td>
</tr>
<tr>
<td>•</td>
<td>Chronic  Day 100 ≥</td>
</tr>
</tbody>
</table>

## Acute Graft vs Host Disease

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| •      | 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

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>HLA disparity  6/6 &gt; 5/6 &gt; 4/6</td>
</tr>
<tr>
<td>•</td>
<td>Allo stem cell source  MRD &gt; UCB &gt; UBM</td>
</tr>
<tr>
<td>•</td>
<td>Donor Age</td>
</tr>
<tr>
<td>•</td>
<td>Sex incompatibility</td>
</tr>
<tr>
<td>•</td>
<td>CMV incompatibility</td>
</tr>
<tr>
<td>•</td>
<td>Immune suppression</td>
</tr>
</tbody>
</table>

## Common Prophylactic Immune Suppressants

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>•</td>
<td>Methotrexate (MTX)</td>
</tr>
<tr>
<td>•</td>
<td>Cyclosporine (CSP)</td>
</tr>
<tr>
<td>•</td>
<td>Prednisone (PDN)</td>
</tr>
<tr>
<td>•</td>
<td>Tacrolimus (FK506)</td>
</tr>
<tr>
<td>•</td>
<td>Mycophenolate Mofetil (MMF)</td>
</tr>
<tr>
<td>•</td>
<td>Anti Thymocyte Globulin (ATG)</td>
</tr>
<tr>
<td>•</td>
<td>Alemtuzumab (Campath)</td>
</tr>
<tr>
<td>•</td>
<td>T-Cell Depletion</td>
</tr>
</tbody>
</table>

## Essential Components Required for GVHD
**Risk of Acute GVHD and HLA Disparity**

Beatty et al. NEJM. 313; 765, 1985

**Chronic GVHD**

- **Skin:** Rash (lichenoid, sclerodermatous, hyper/hypo-pigmented, flaky), Alopecia
- **Joints:** Arthralgia, arthritis, contractures
- **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

**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

**Summary**

- T-cell activation & proliferation requires immunological synapse with TCR/MHC and co-simulating ligands & receptors
- Tissue rejection maybe 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.