Transplantation Immunology

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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

- T cell contact residue of peptide
- Polymorphic residue of MHC
- Anchor residue of peptide
- "Pocket" of MHC
Direct and Indirect AlloAntigen Recognition

**Direct allore cognition**
- Donor dendritic cell
- Donor MHC + peptide
- Recipient CD4^+ T cell
- Predominant role in acute rejection

**Indirect allore cognition**
- Uptake
- Processing
- Recipient dendritic cell
- 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

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

[Diagram showing regulation process]
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)
  - 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

**Solid Organ**
- **Hyperacute**
  - Minutes to hours
  - Preexisting antibodies (IgG)
  - Intravascular thrombosis
  - Hx of blood transfusion, transplantation or multiple pregnancies

- **Acute Rejection**
  - Few days to weeks
  - CD4+ CD8 T-Cells
  - Humoral antibody response
  - Parenchymal damage & Inflammation

- **Chronic Rejection**
  - Chronic fibrosis
  - Accelerated arteriosclerosis
  - 6 months to yrs
  - CD4, CD8, (Th2)
  - Macrophages

**Bone Marrow/PBSC**
- **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

- **Not Applicable**
Immune Mechanisms of Solid Organ Allograft Rejection

Hyperacute, Acute, Chronic Kidney Allograft Rejection
Mechanisms of Acute 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 synthase
  - 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)

- Blocks B7 Co-Stimulation
  - CTLA-4-Ig
  - Inhibits 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

![Graph showing the incidence of renal allograft survival in relation to the number of mismatched HLA alleles.](image)
Mechanism of T-Cell Activation vs Tolerance

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)
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

<table>
<thead>
<tr>
<th>Component</th>
<th>Criteria</th>
</tr>
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<tbody>
<tr>
<td>Myeloid</td>
<td>Absolute neutrophil count ≥ 500/mm³ x 2 days after nadir</td>
</tr>
<tr>
<td>Platelet</td>
<td>Platelets ≥ 20 k/mm³ x 7 days untransfused after nadir</td>
</tr>
</tbody>
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### 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
### Graft vs Host Disease

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration</th>
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<tbody>
<tr>
<td>Hyperacute</td>
<td>Day 0 – 7</td>
</tr>
<tr>
<td>Acute</td>
<td>Day 7 – 100</td>
</tr>
<tr>
<td>Chronic</td>
<td>Day 100 &gt;</td>
</tr>
</tbody>
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### Acute Graft vs Host Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dermal (Skin)</strong></td>
<td>Maculopapular, Palms / Soles, Pruritic ±, Cheeks/ Ears/ Neck / Trunk, Necrosis / Bullae</td>
</tr>
<tr>
<td><strong>Hepatic</strong></td>
<td>Hyperbilirubinemia, Transaminemia</td>
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<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Diarrhea, Abdominal pain, Vomiting, Nausea</td>
</tr>
</tbody>
</table>
### 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, 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.