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)
Innate & Adaptive Immunity

**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

Developmental Dendritic Cell Formation

Wu et al. Immunity, 2007
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)
  • 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)**

- **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

- **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

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**Pathological Mechanism of Rejection**

<table>
<thead>
<tr>
<th>Solid Organ</th>
<th>Bone Marrow/PBSC</th>
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<tr>
<td><strong>Hyperacute</strong></td>
<td>Not Applicable</td>
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<tr>
<td>- Minutes to hours</td>
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Immune Mechanisms of Solid Organ Allograft Rejection

Hyperacute, Acute, Chronic Kidney Allograft Rejection

Hyperacute, Acute, Chronic Kidney 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
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

Mechanisms of T-Cell Immunosuppressants
Incidence of Renal Allograft Survival in Influenced by HLA Matching

Mechanism of T-Cell Activation vs Tolerance
Mechanisms of T-Cell Activation vs. Inhibition

Foxp3+ Regulatory T-Cells Inhibit Naïve T-Cell Differentiation

Sakaguchi et al Science, 2007
Human Natural Killer Cells

**Immunoregulatory NK Cell**
- CD56<sup>bright</sup>
- CD16<sup>dim/neg</sup>
- CD16<sup>bright</sup>
- GM-CSF
- IFN-γ

**Cytotoxic NK Cell**
- CD56<sup>dim</sup>
- CD16<sup>bright</sup>
- IL-2, IL-15Rβγc
- KIR
- NKRs
- CD94/NKG2A

**Effector Functions**
- ADCC
- LAK
- Natural Cytotoxicity

**High Cytokine Production**
- IFN-γ
- IL-10

**Model of Human NK Cell Development**


NK Cell Interaction with DC and T-Cells

Regulation of NK Cell Activation vs. Inhibition
Regulation of NK Cell Activation and Inhibition

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 $\geq 500/\text{mm}^3$ x 2 days after nadir

- **Platelet**
  - Platelets $\geq 20 \text{ k/mm}^3$ x 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

**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)
- Tacroliimus (FK506)
- Mycophenolate Mofitel (MMF)
- Anti Thymocyte Globulin (ATG)
- Alemtuzamab (Campath)
- T-Cell Depletion

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.