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)

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

Dranoff et al Nature Reviews Cancer, 4: 11; 2004

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

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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)
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

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

Antigen Recognition & Immunological Synapse

Mixed Lymphocyte Reaction (MLR)

Pathological Mechanism of Rejection

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<th>Solid Organ</th>
<th>Bone Marrow/PBSC</th>
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• Hyperacute
  - Minutes to hours
  - Preexisting antibodies (IgG)
  - Intravascular thrombosis
  - History 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 atherosclerosis
  - 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
**Immune Mechanisms of Solid Organ 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)

**Hyperacute, Acute, Chronic Kidney Allograft Rejection**

- **Inhibition of mTOR**
  - Rapamycin binds to FKBP
  - Inhibits IL-2 signaling
- **Antibodies to T-Cells**
  - OKT3 (Anti-CD3)
  - Daclizumab (Anti-CD25)
- **Confolexoids**
  - Prednisolone/Probenecid
  - Inhibit 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 Acute Allograft Rejection**

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

Mechanism of T-Cell Activation vs. Tolerance

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

Human Natural Killer Cells

Mechanisms of T-Cell Activation vs. Inhibition

Model of Human NK Cell Development
NK Cell Interaction with DC and T-Cells

Caligiuri et al, Blood 2008

Regulation of NK Cell Activation vs. Inhibition

Caligiuri et al, Blood 2008

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

Regulation of NK Cell Activation and Inhibition

Caligiuri et al, Blood 2008

General Indications of Blood and Marrow Transplantation

- Dose intensity for malignant tumor (DI)
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**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)

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**Complications (Acute)**

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

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**Essential Components Required for GVHD**

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

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**Graft vs Host Disease**

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

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**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

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**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

**Chronic GVHD**

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

- 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.