

Transplantation Immunology

Mitchell S. Cairo, MD

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

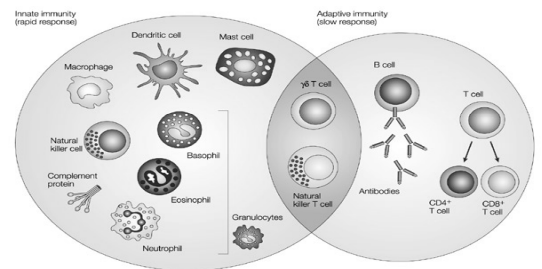
Types of Grafts

- 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)

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)

Innate & Adaptive Immunity



Nature Reviews | Cancer

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

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)

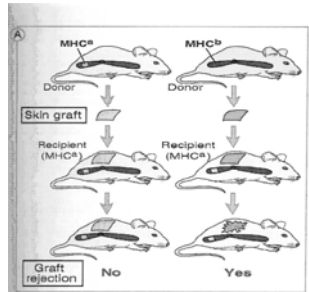
Rejection

- First Set Rejection
 - Skin graft in mice 7-10 days
- Second Set Rejection
 - Skin graft in mice in 2-3 days

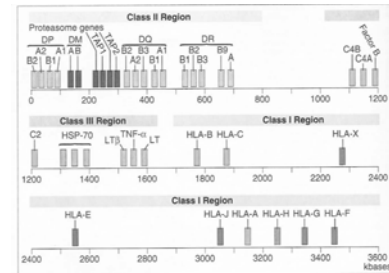
Mechanisms

- Foreign alloantigen recognition
- Memory lymphocytes (adaptive immunity)
- Can be adoptively transferred

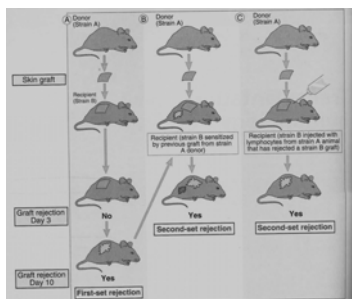
MHC Restricted Allograft Rejection



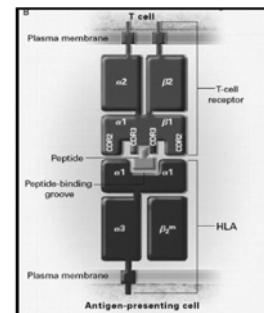
Map of Human MHC



First & Second Allograft Rejection



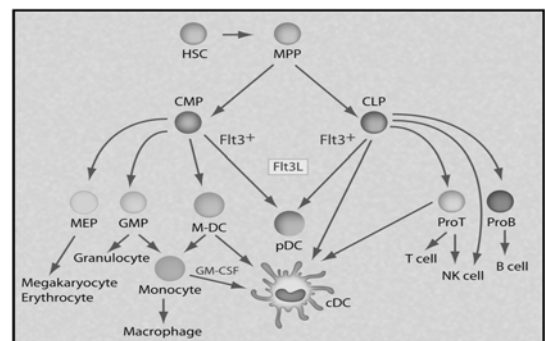
T-Cell Recognition of Peptide-MHC Complex



AlloAntigen Recognition

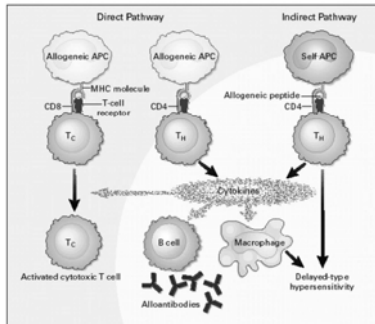
- Major Histocompatibility Complex (MHC)
 - Class I HLA A, B, C bind to TCR on CD8 T-Cell
 - Class II DR, DP, DQ bind to TCR on CD4 T-Cell
 - Most polymorphic genes in human genome
 - Co-dominantly expressed
- Direct presentation (Donor APC)
 - Unprocessed allogeneic MHC
- Indirect presentation (Host APC)
 - Processed peptide of allogeneic MHC

Developmental Dendritic Cell Formation



Wu et al Immunity, 2007

Direct and Indirect AlloAntigen Recognition



Mixed Lymphocyte Reaction (MLR)

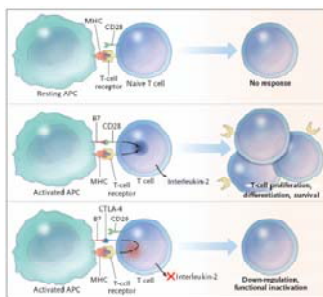
Definition & Mechanism

- *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

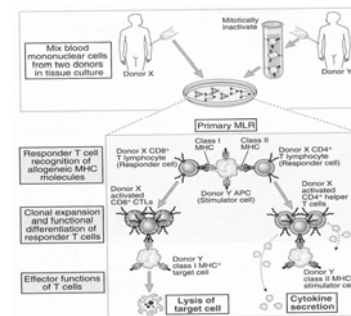
- Can be adoptively transferred
- Require co-stimulation
- Require MHC
- Require Class I differences for CD8 T-cell response
- Require Class II differences for CD4 T-cell response

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

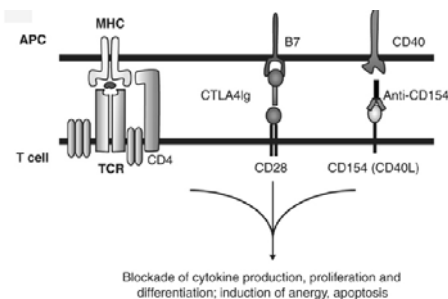


Sharpe et al, NEJM, 2006

Mixed Lymphocyte Reaction (MLR)



Antigen Recognition & Immunological Synapse



Pathological Mechanism of Rejection

Solid Organ

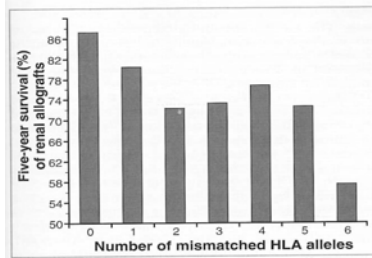
- Hyperacute
 - Minutes to hours
 - Preexisting antibodies (IgG)
 - Intravascular thrombosis
 - Hx of blood transfusion, transplantation or multiple pregnancies
- Acute Rejection
 - Few days to weeks
 - CD4 + CD8 T-Cells
 - Humoral antibody response
 - Parenchymal damage & Inflammation
- Chronic Rejection
 - Chronic fibrosis
 - Accelerated arteriosclerosis
 - 6 months to yrs
 - CD4, CD8, (Th2)
 - Macrophages

Bone Marrow/PBSC

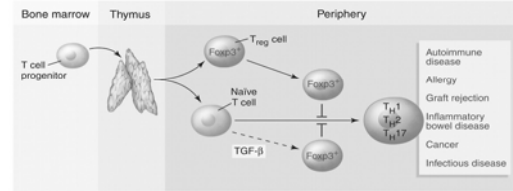
Not Applicable

- 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

Incidence of Renal Allograft Survival in Influenced by HLA Matching

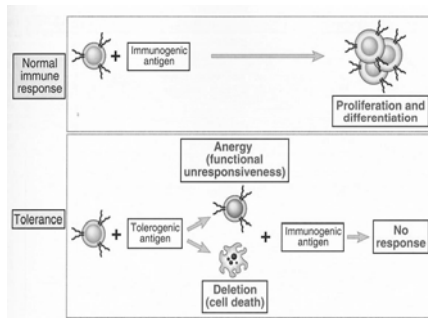


Foxp3⁺ Regulatory T-Cells Inhibit Naïve T-Cell Differentiation



Sakaguchi et al Science, 2007

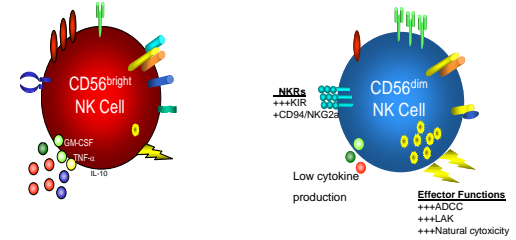
Mechanism of T-Cell Activation vs Tolerance



Human Natural Killer Cells

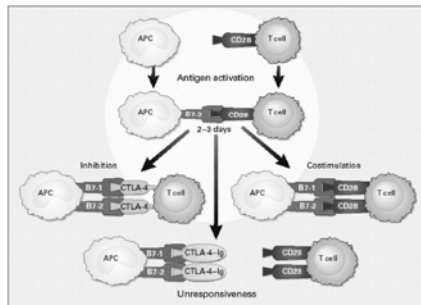
Immunoregulatory NK Cell

Cytotoxic NK Cell

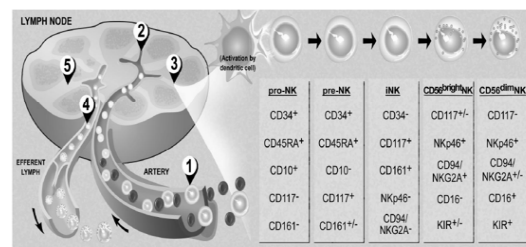


Farag/Caligiuri MA, *Bld Rev*, 20: 123,2006

Mechanisms of T-Cell Activation vs. Inhibition

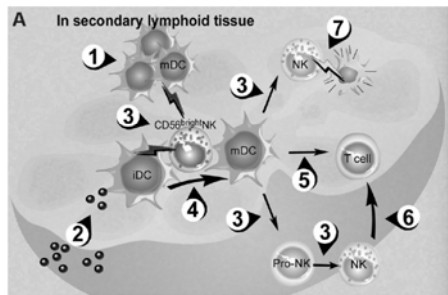


Model of Human NK Cell Development



Caligiuri et al, *Blood* 2008

NK Cell Interaction with DC and T-Cells

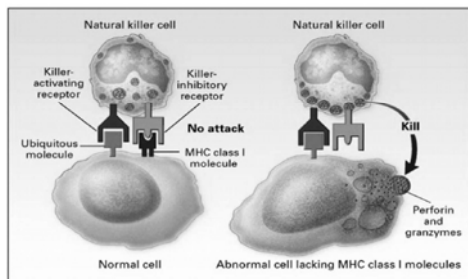


Caligiuri et al, Blood 2008

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

Regulation of NK Cell Activation vs. Inhibition

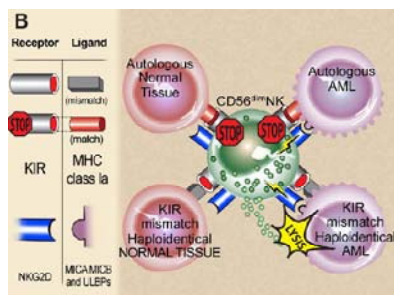


Specific Indications (Pediatric)

Malignant

- Leukemia
- Solid Tumors
- Lymphomas

Regulation of NK Cell Activation and Inhibition



Caligiuri et al, Blood 2008

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 $\geq 20 \text{ k}/\text{mm}^3$ x 7 days untransfused after nadir
Chimerism (Allogeneic)	
• Fluorescence <i>in situ</i> Hybridization (FISH) (Sex mismatch)	
• VNTR	(Molecular)

Graft vs Host Disease	
• Hyperacute	Day 0 – 7
• Acute	Day 7 – 100
• Chronic	Day 100 \geq

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

Acute Graft vs Host Disease	
• Dermal (Skin) :	Maculopapular Palms / Soles Pruritic \pm Cheeks/ Ears/ Neck / Trunk Necrosis / Bullae
• Hepatic :	Hyperbilirubinemia Transaminemia
• Gastrointestinal :	Diarrhea Abdominal pain Vomiting Nausea

Essential Components Required for GVHD
<ul style="list-style-type: none"> • Immuno-incompetent host • Infusion of competent donor T-cells • HLA disparity between host and donor

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

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.

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