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)

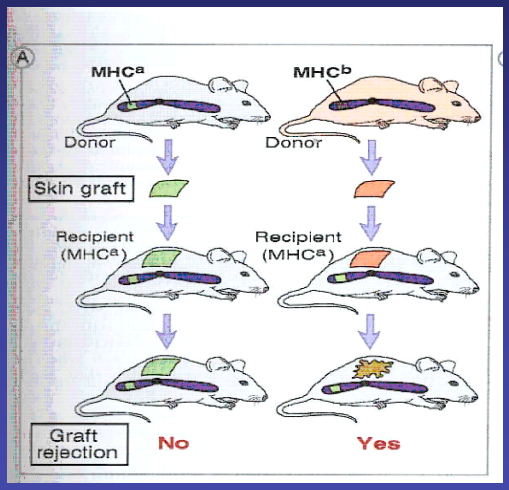
Rejection

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

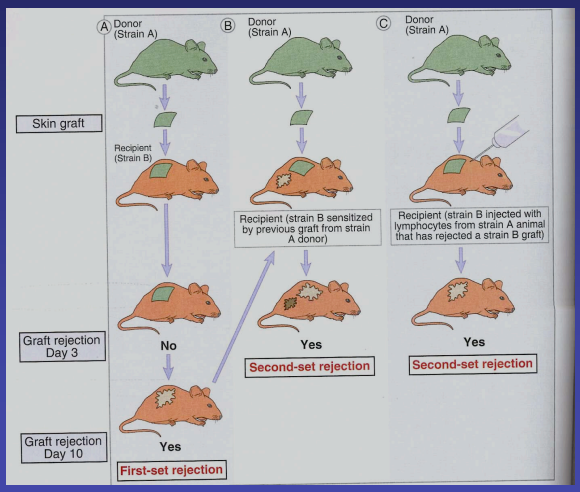
Mechanisms

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

MHC Restricted Allograft Rejection



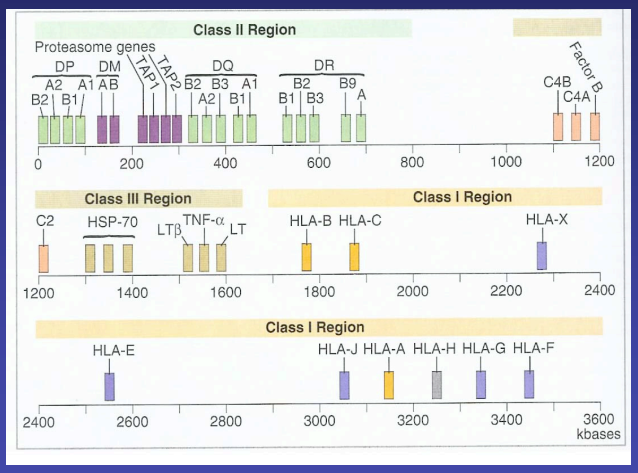
First & Second Allograft Rejection



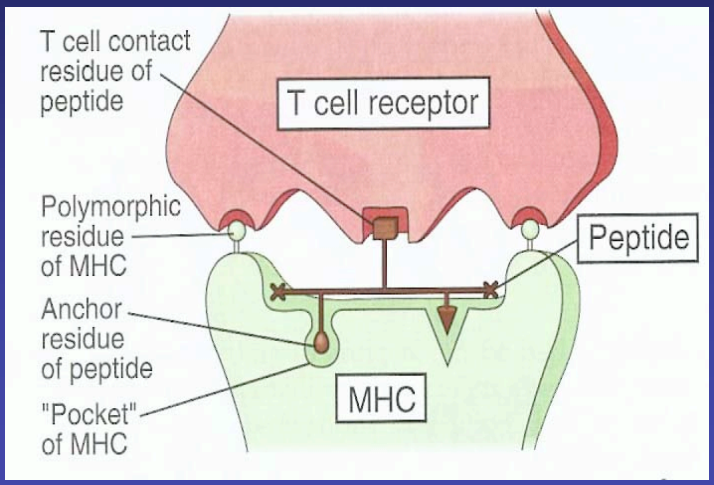
AlloAntigen Recognition

- 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

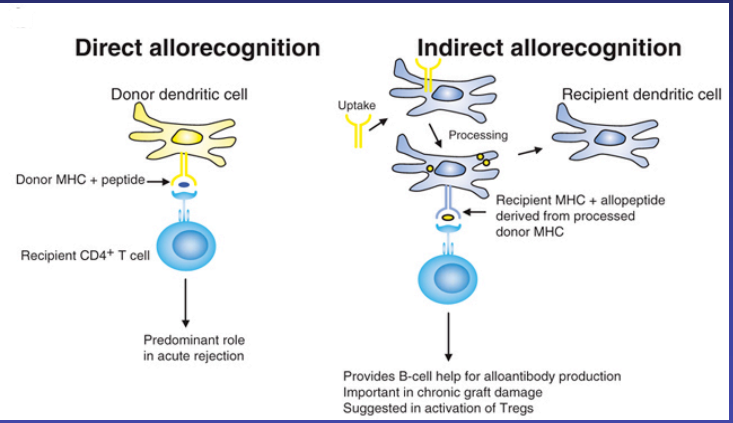
Map of Human MHC



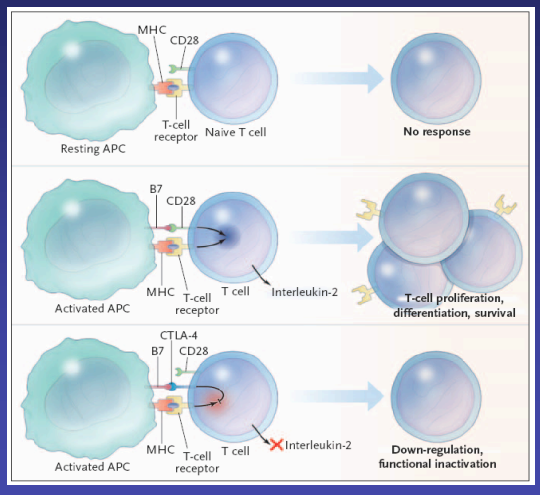
T-Cell Recognition of Peptide-MHC Complex



Direct and Indirect AlloAntigen Recognition

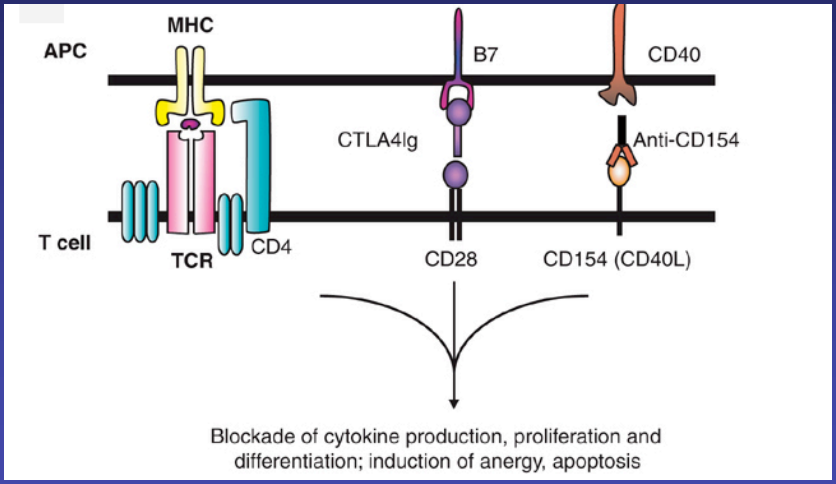


Regulation of T-cell Activation and Tolerance by B7- CD28/CTLA-4 Pathway



Sharpe et al, NEJM, 2006

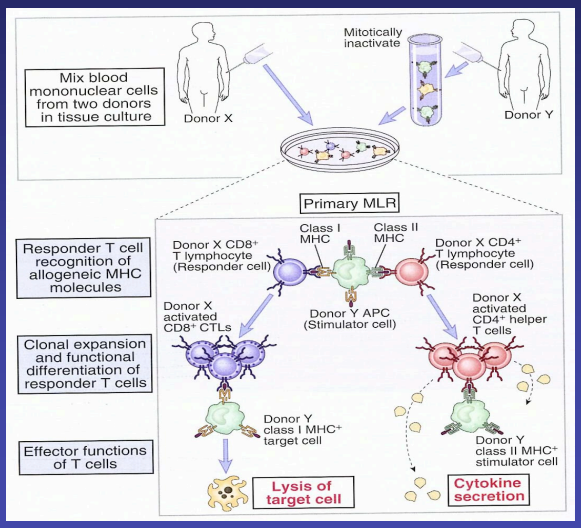
Antigen Recognition & Immunological Synapse



Mixed Lymphocyte Reaction (MLR)

- **Definition & Mechanism**
  - *In vitro* test of T-cell regulation of allogeneic MHC
  - Stimulators (donor-irradiated monnuclear 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

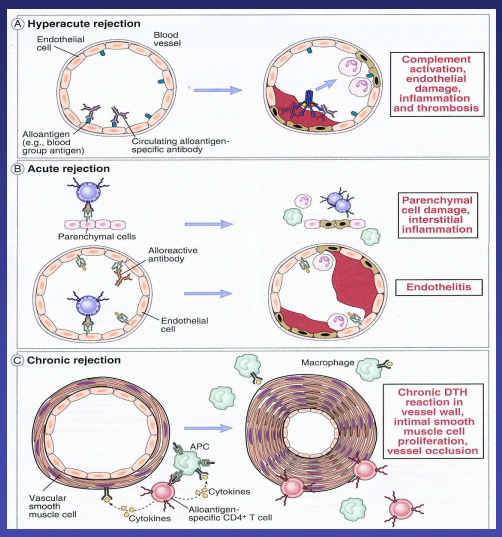
- Hyperacute
  - Minutes to hours
  - Preexisting antibodies (IgG)
  - Intravascular thrombosis
  - Hx of blood transfusion, transplantation or multiple pregnancies
- Acute Rejection
  - Few days to weeks
  - CD4 + CD8 T-Cells
  - Humoral antibody response
  - Parenchymal damage & Inflammation
- Chronic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

Bone Marrow/PBSC

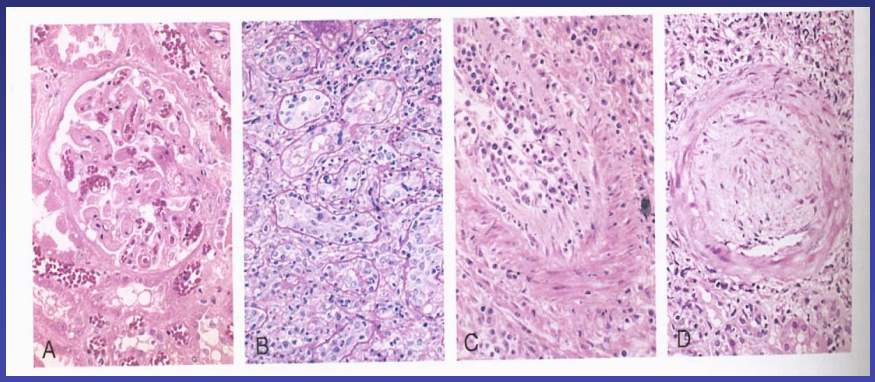
Not Applicable

- 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

Immune Mechanisms of Solid Organ Allograft Rejection

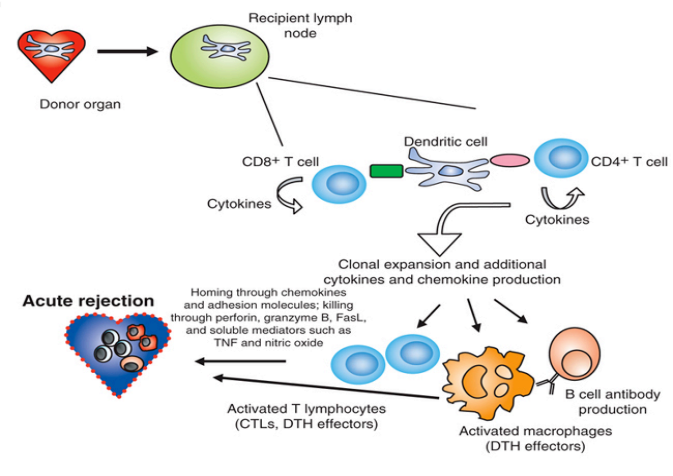


Hyperacute, Acute, Chronic Kidney Allograft Rejection



Hyperacute | Acute | Acute | Chronic

Mechanisms of Acute Allograft Rejection



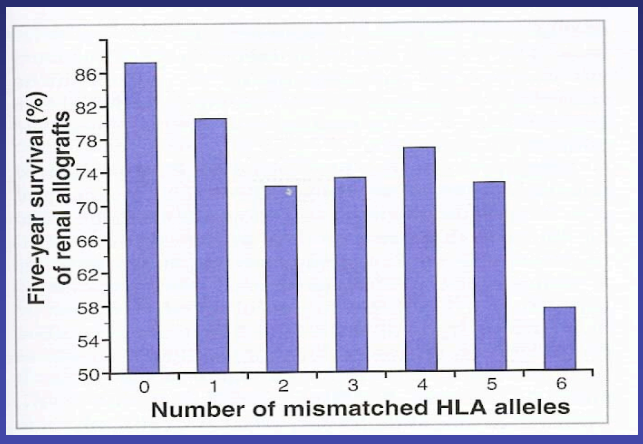
Prevention & Treatment of Allograft Rejection

- ABO Compatible
  (Prevent hyperacute rejection in solid organs)
  (Prevent transfusion reaction in BM/PBSC)
- MHC allele closely matched
- Calcineurin inhibitors
  - Cyclosporine binds to Cyclophillin
  - 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)

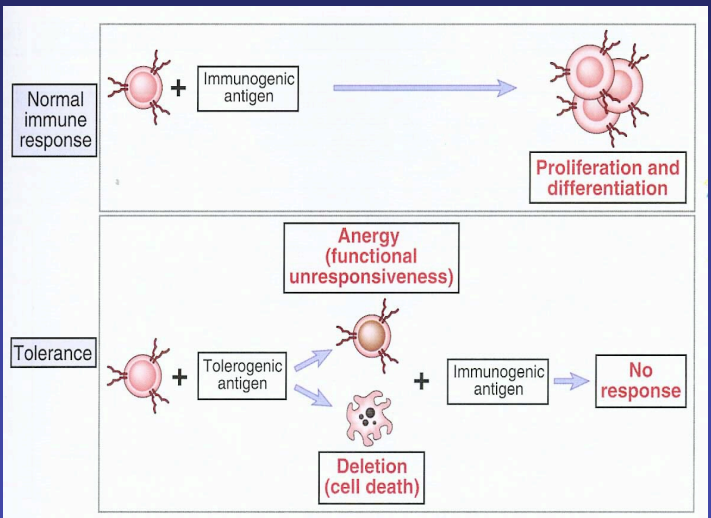
Prevention & Treatment of Allograft Rejection

- Inhibition of mTOR
  - Rapamycin binds to FKBP
  - Inhibits mTOR
  - Inhibits IL-2 signaling
- Antibodies to T-Cells
  - OKT3 (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



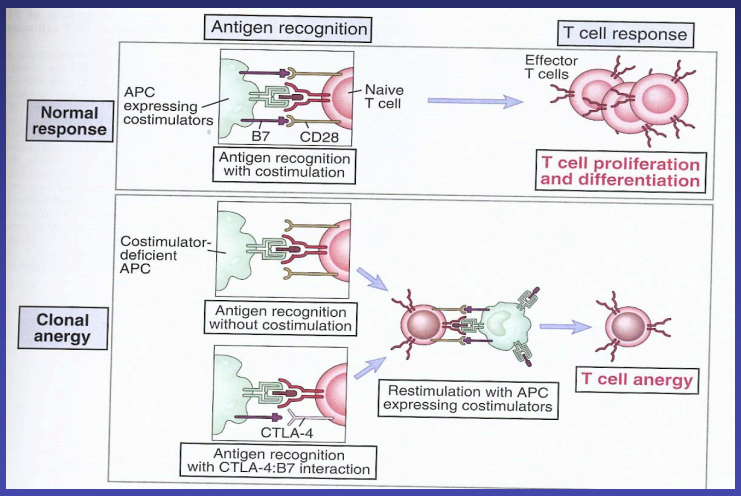
Mechanism of T-Cell Activation vs Tolerance



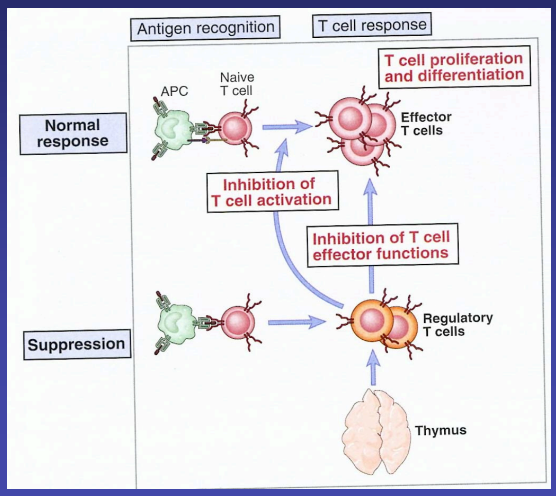
Immunological Tolerance

- Immunological specific recognition of self antigen by specific lymphoytes
- Central tolerance (Thymus-dervived)
  - 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 vsTumor (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 neutophil count ≥ 500/mm^3 x 2 days after nadir
- Platelet — Platelets ≥ 20 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

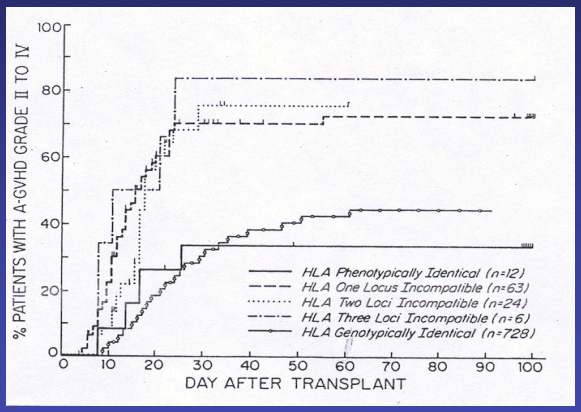
Risk Factors of GVHD

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

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 (preexsisting 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.