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)

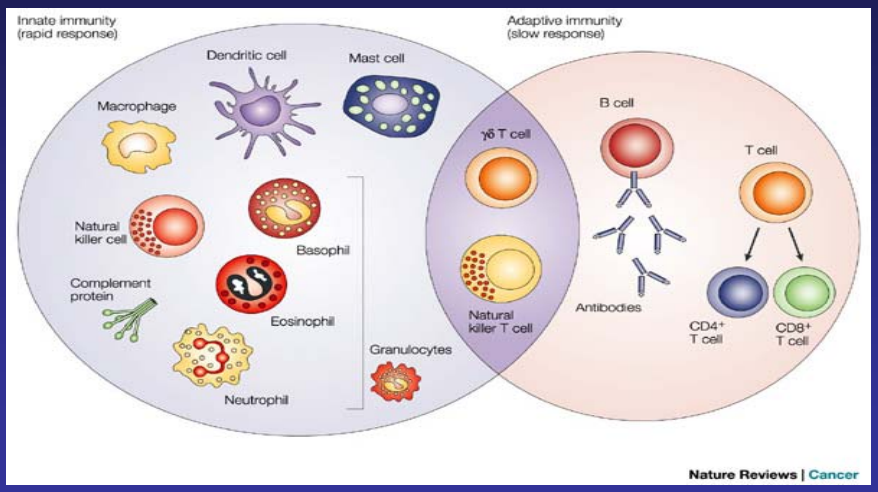
Objectives

- 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



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

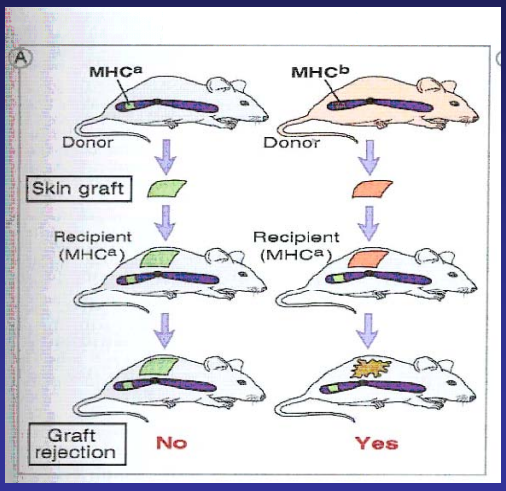
Rejection

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

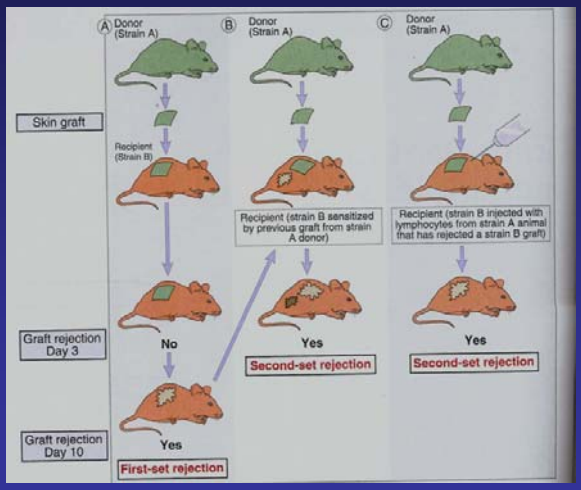
Mechanisms

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

MHC Restricted Allograft Rejection



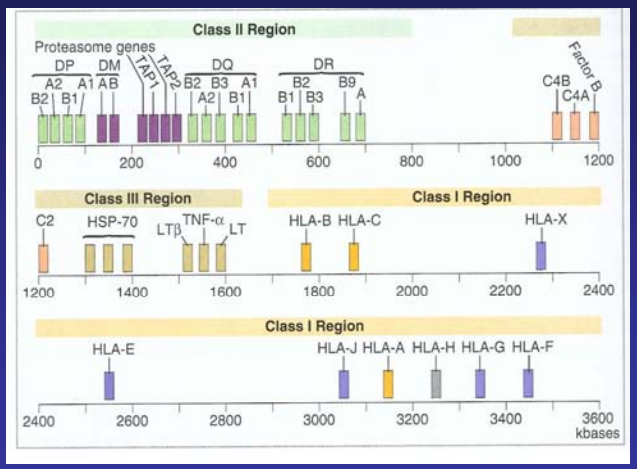
First & Second Allograft Rejection



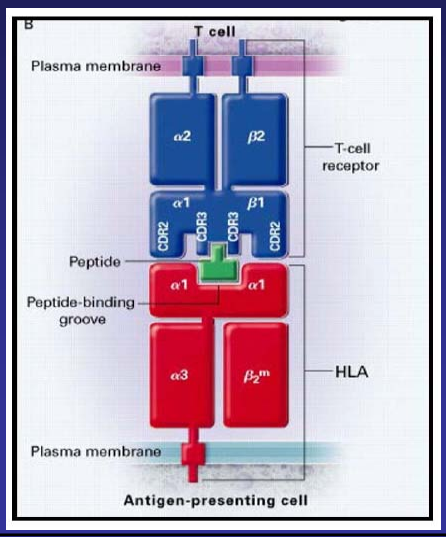
AlloAntigen Recognition

- 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

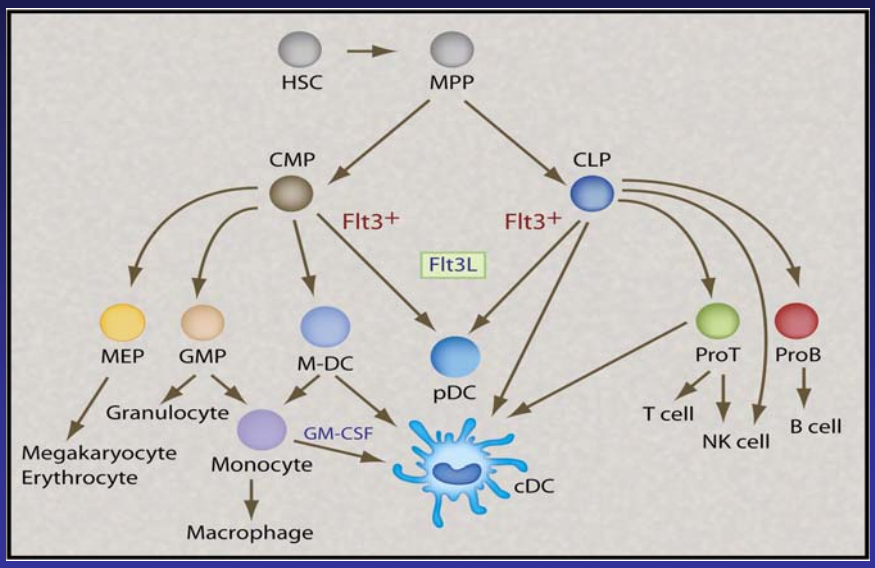
Map of Human MHC



T-Cell Recognition of Peptide-MHC Complex

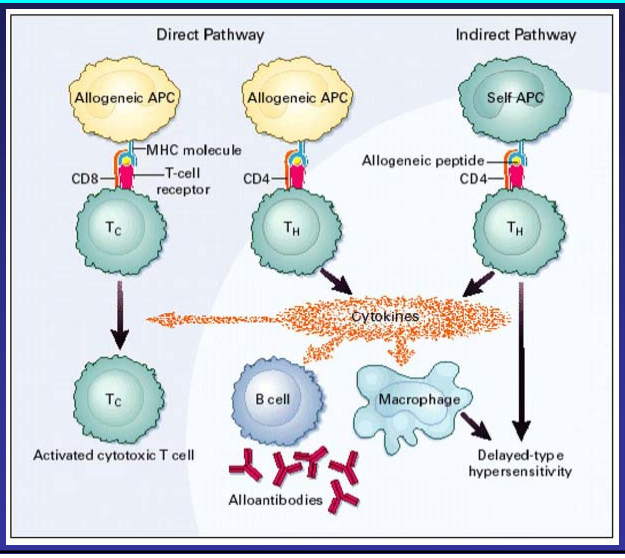


Developmental Dendritic Cell Formation

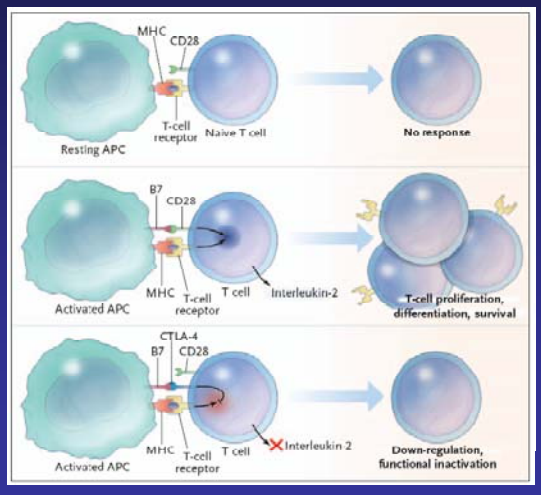


Wu et al Immunity, 2007

Direct and Indirect AlloAntigen Recognition

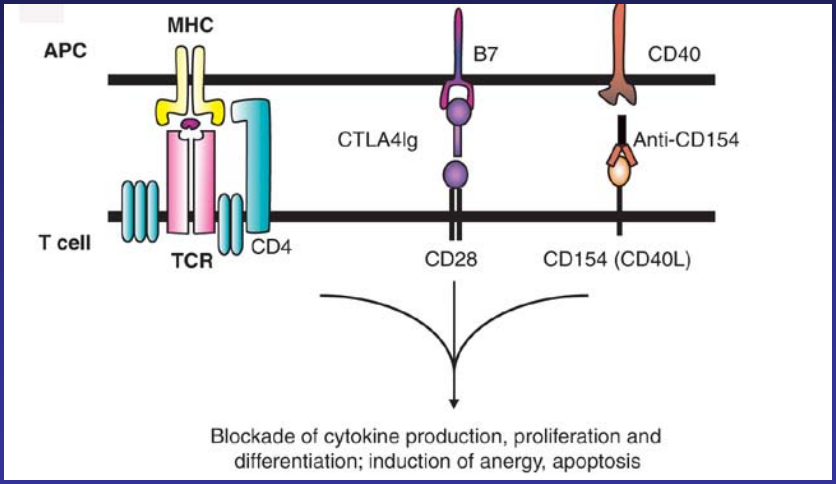


Regulation of T-cell Activation and Tolerance by B7- CD28/CTLA-4 Pathway



Sharpe et al, NEJM, 2006

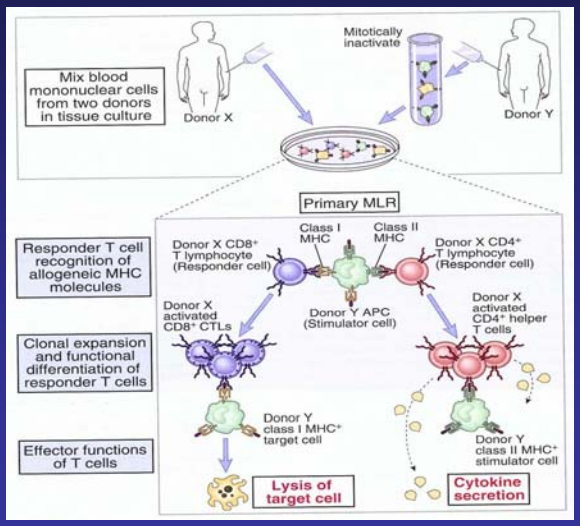
Antigen Recognition & Immunological Synapse



Mixed Lymphocyte Reaction (MLR)

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

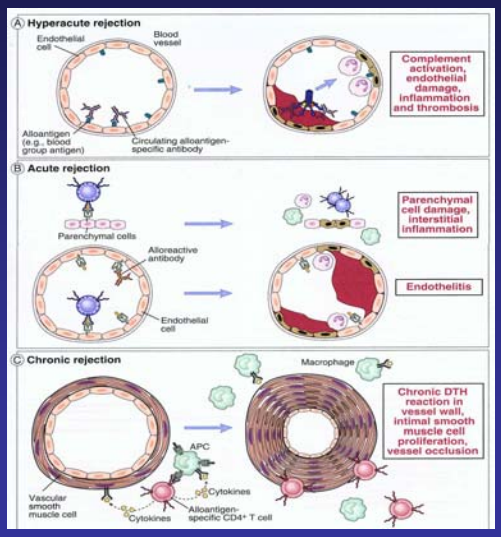
- Hyperacute
  - Minutes to hours
  - Preexisting antibodies (IgG)
  - Intravascular thrombosis
  - Hx of blood transfusion, transplantation or multiple pregnancies
- Acute Rejection
  - Few days to weeks
  - CD4 + CD8 T-Cells
  - Humoral antibody response
  - Parenchymal damage & Inflammation
- Chronic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

Bone Marrow/PBSC

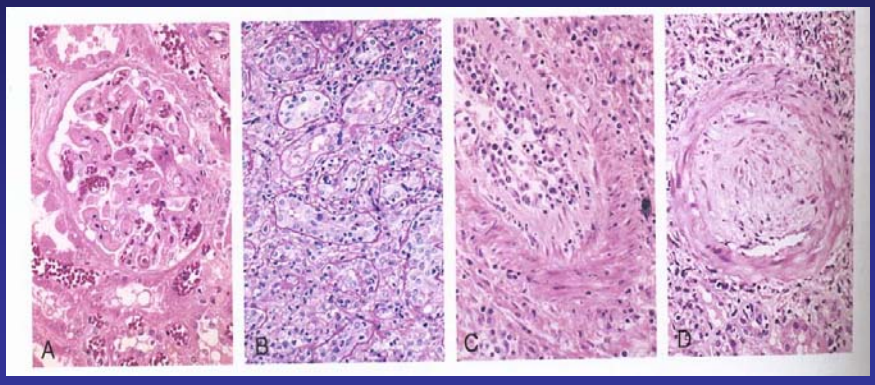
Not Applicable

- 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

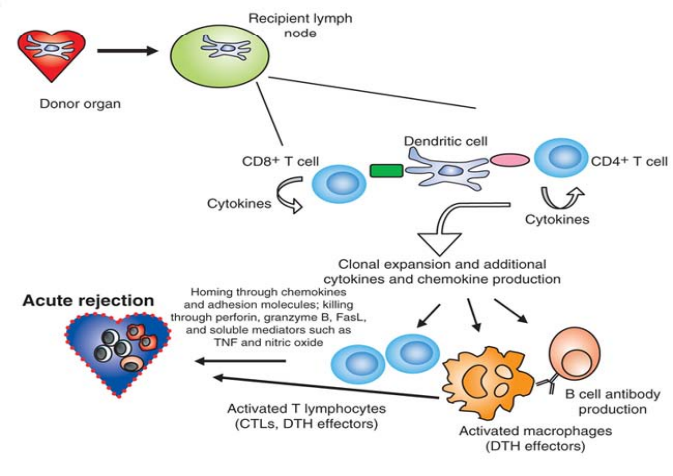


Hyperacute, Acute, Chronic Kidney Allograft Rejection



Hyperacute | Acute | Acute | Chronic

Mechanisms of Acute Allograft Rejection



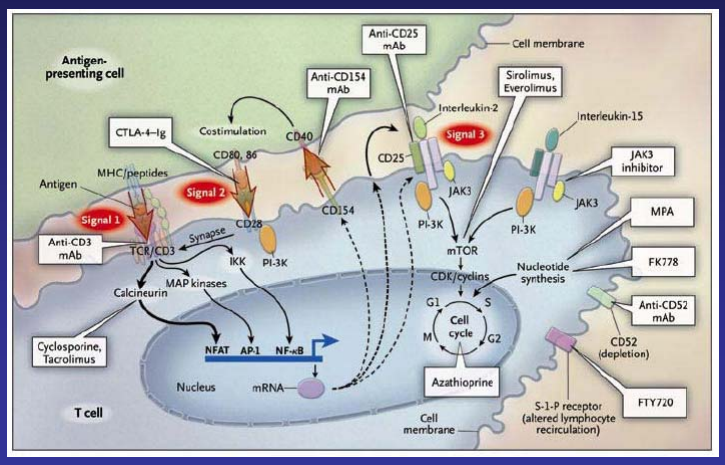
Prevention & Treatment of Allograft Rejection

- 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)

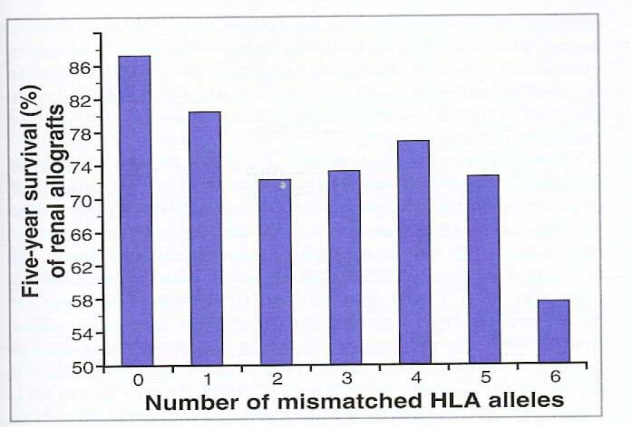
Prevention & Treatment of Allograft Rejection

- 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

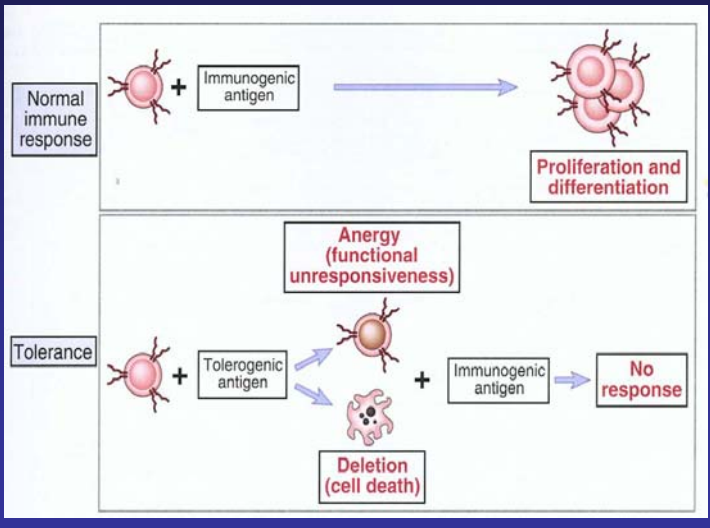
Mechanisms of T-Cell Immunosuppressants



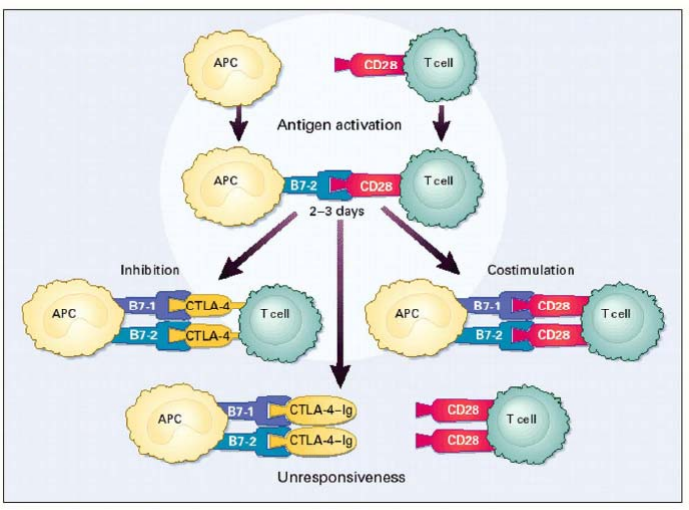
Incidence of Renal Allograft Survival in Influenced by HLA Matching



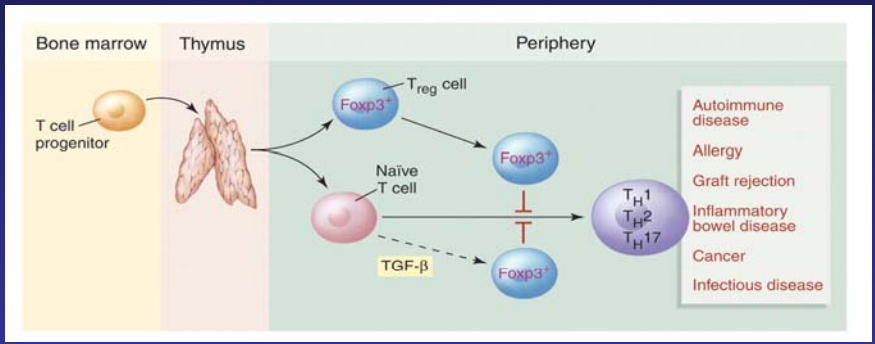
Mechanism of T-Cell Activation vs Tolerance



Mechanisms of T-Cell Activation vs. Inhibition

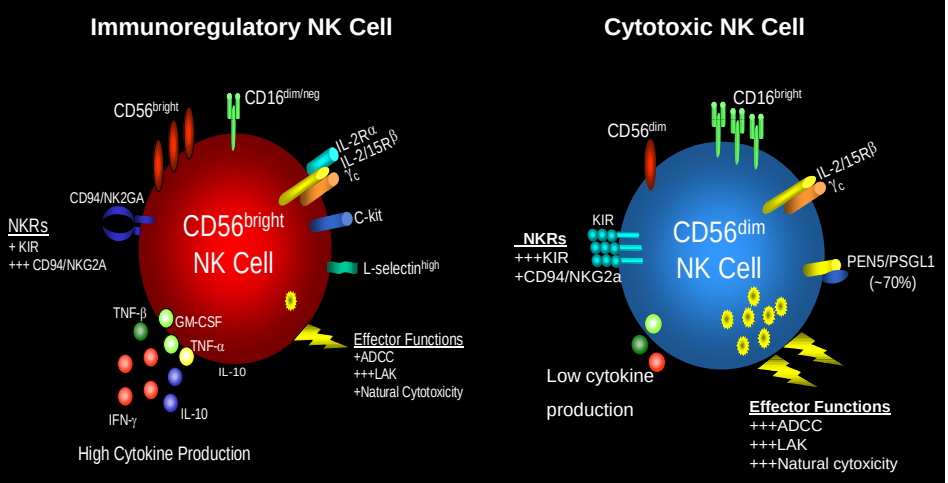


Foxp3$^+$ Regulatory T-Cells Inhibit Naïve T-Cell Differentation



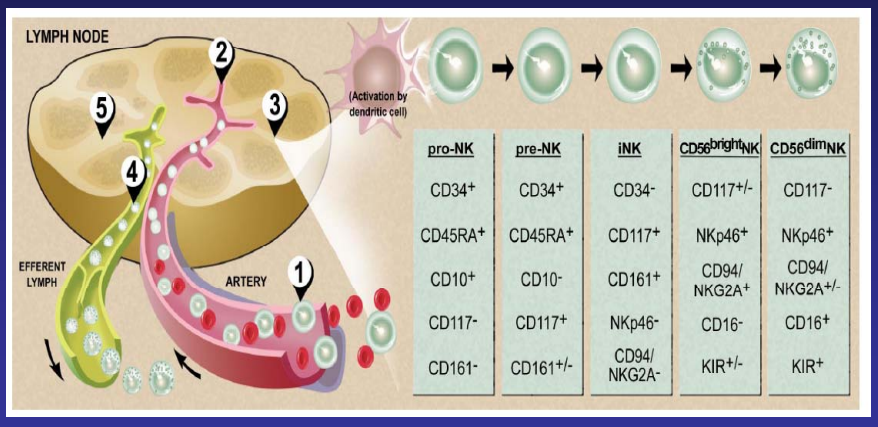
Sakaguchi et al Science, 2007

Human Natural Killer Cells



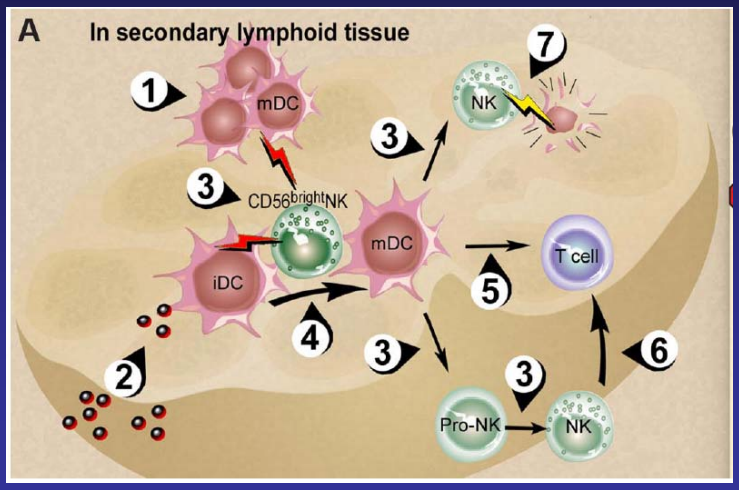
Farag/Caligiuri MA, ***Bld Rev, 20: 123,2006***

Model of Human NK Cell Development



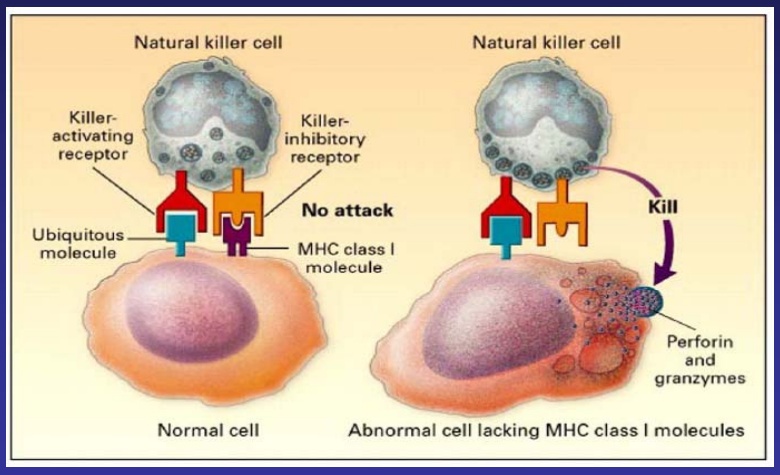
Caligiuri et al, Blood 2008

NK Cell Interaction with DC and T-Cells

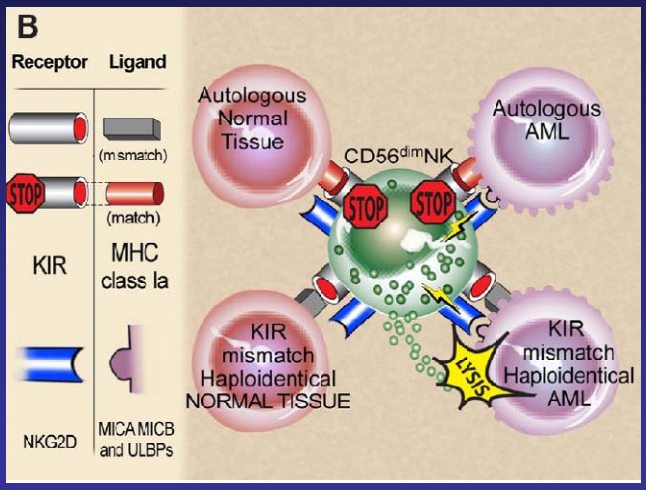


Caligiuri et al, Blood 2008

Regulation of NK Cell Activation vs. Inhibition



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)
- 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

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.