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Transplant Surgery and Immunology

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Assistant Professor of Transplant Surgery

Fall 2008
Renal Transplantation
Technical Consideration
Surgical Complications

• Vascular
  – Arterial
  – Venous
• Ureteral leak/stenosis
• Wound
  – Hematoma
  – Lymphocele
Implantation of the pancreas allograft in the right side

- Vena cava
- Aorta
- Allograft pancreas
- Celiac axis or iliac "Y" graft
- Portal vein
- Stomach
- Recipient small bowel
- Common iliac vessels
- Allograft Duodenum
Transplant Immunology

The Biology of the Alloresponse
Learning Objectives

• To understand the role of the MHC
• To understand the 3 signals needed for T-cell activation
• To understand the mechanisms of transplant rejection
• To understand how transplant rejection is prevented
Thymic Selection

A. Lack of positive selection
- Thymic epithelial cell
- CD4+CD8+ thymocyte
- CD4
- CD8

Failure to recognize peptide-MHC complex on thymic epithelial cell
- Apoptotic cell death

B. Positive selection
- Thymic epithelial cell
- CD4+CD8+ thymocyte
- CD4
- CD8
- Class II MHC

Low-affinity/avidity recognition of peptide-MHC complex on thymic epithelial cell
- Rescue from programmed cell death; conversion to single positive

C. Negative selection
- Thymic antigen-presenting cell
- CD4+CD8+ thymocyte
- CD4
- CD8
- Class II MHC

High-avidity recognition of peptide-MHC complex on thymic antigen-presenting cell
- Apoptotic cell death
Central Paradigm for Cellular Initiation of an Immune Response
• MHC I antigen processing
  A Protein
  B Proteasome
  C MHC class I protein synthesis
  D Peptides for presentation
  E ER
  F Plasma membrane
1. Ubiquitination
2. Protein degradation to peptides by proteasome
3. Transporting peptides to the lumen of ER by ABC transporters
4. Binding of peptides in a groove of MHC I complex
5. Antigen presentation on plasma membrane

• MHC II antigen processing
  A Foreign protein
  B Endosome
  C Lysosome
  D Late endosome/Phagolysosome
  E Rough ER
  F Golgi apparatus
  G CLIP for antigen exchange
  H Antigen presentation at plasma membrane

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Antigen Presenting Cells

• Dendritic cells
• Macrophages
• B Lymphocytes
• Vascular endothelial cells
• Various epithelial and parenchymal cells
Antigen Presentation on APC

• Occurs through the major histocompatibility complex (MHC)

• The MHC are a group of genes that are responsible for the recognition of the graft as foreign

• The principal function of MHC is to present foreign antigen fragments that can be recognized by specific antigen receptors on T cells
MHC Class I and Class II

[Diagram showing MHC Class I and Class II structures with peptide-binding regions and A, B, C, DR, DQ, DP, HLA, and GLO regions.]
MHC Class I Molecule (HLA A2)
MHC Class I and II

- Class I is presented on all nucleated cells and recognized by CD8+ T cells

- Class II is presented on APC and recognized by CD4+ T cells
Human Leukocyte Antigen (HLA)

HLA’s are polymorphic cell-surface molecules (alloantigens) that are encoded by the MHC genes.
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Antigens listed in parentheses are the broad antigens; antigens followed by broad antigens in parentheses are the antigen splits.
MHC Polymorphism

• MHC molecules are highly polymorphic to allow extraordinary levels of diversity in functionally important regions (peptide binding site) without losing structural integrity.

• The large number of polymorphic MHC molecules expressed by an individual permits binding of an extensive range of structurally different peptides.
Three Signals of Tcell Activation

• Antigen presentation and recognition (provides specificity – essential but not sufficient)

• Costimulation – needed for T-cell proliferation

• Autocrine proliferation
Role of Co-stimulation in T Cell Activation

A. Antigen recognition

"Resting" (costimulator-deficient) APC

Naive T cell

T cell response

No response

B. Activation of APCs by microbes, innate immune response

Activated APCs: increased expression of costimulators, secretion of cytokines

Cytokines (e.g., IL-12)

B7

CD28

Effecter T cells

T cell proliferation and differentiation

IL-2
The image depicts a diagram illustrating the interaction between T cells and APCs (Antigen Presenting Cells). It shows the pathway of antigen presentation and the differentiation of T cells.

1. Donor Ag, which is the antigen presented by the APC.
2. MHC class II antigen binding to the TCR (T-cell receptor) on the T cell.
3. CD4 and CD28 molecules on the T cell surface.
4. T cell activation and the subsequent events leading to anergic T cells or proliferation and differentiation to effector T cells.

The diagram highlights the role of B7 molecules in the costimulation of T cell activation.
Intracellular signaling pathways in T cell activation

ANTIGEN PRESENTING CELL

FIRST SIGNAL

TD T CELL

SECOND SIGNAL

Tyrosine kinase

PLC C\textsubscript{Y1}

PIP\textsubscript{2}

DAG

IP\textsubscript{3}

Intracellular Ca\textsuperscript{2+}

Calcineurin

NFAT\textsubscript{p}

NFAT\textsubscript{p}

NFAT\textsubscript{p}

INDUCTION OF CYTOKINE GENES AND OTHER T CELL ACTIVATION GENES

CD28RC

PKC

Jun

Fos

Source Undetermined
Allorecognition
Direct vs Indirect