Transplantation Immunology

Ali Al Khader, MD
Faculty of Medicine
Al-Balqa’ Applied University
Email: ali.alkhader@bau.edu.jo
Introduction

- Graft rejection is mediated by both cell- and antibody-mediated reactions
- Much of knowledge came from studies on mice
- Grafts among members of one inbred strain are accepted and grafts from one strain to another are rejected
- The products of many of the genes that control graft rejection are expressed in all tissues
- “Syngeneic” VS “Allogeneic” VS “Xenogeneic”
Introduction, cont’d

- Every person expresses six class I MHC alleles (one allele of HLA-A, -B, and -C from each parent).
- More than eight class II MHC alleles.
- High polymorphism...thousands of different alleles of each gene in the population.
- We need to develop therapies to prevent or minimize rejection.

Products of these genes are the main molecules recognized in rejection.
Recognition of allograft antigens
Direct recognition

• Foreign MHC with any peptide are recognized as self MHC with foreign peptide → cross-reactivity

• These MHCs are mainly carried by dendritic cells

• CD8+ or CD4+ T cells are activated according to the type of MHC that is recognized

Inflammation & antibody secretion
Indirect recognition

• Donor MHCs are processed by host APCs then their peptides are presented by host’s MHC II expressed on host’s APCs

CD4+ T cells are activated → Inflammation & antibody secretion
Mechanisms of rejection

• T cell-mediated rejection:
  ...CTLs  →  Death of parenchymal cells
  Death of endothelial cells  →  Thrombosis and graft ischemia

...Helper T cells  ➔  inflammation (delayed type hypersensitivity reaction)
  →  Death of parenchymal cells
  Death of endothelial cells  →  Thrombosis and graft ischemia
Mechanisms of rejection, cont’d

• Antibody-mediated rejection:

...alloantibodies against graft MHC molecules and other alloantigens
...actions mainly on endothelium...by activating complement and recruitment of leukocytes

Death of endothelial cells

Thrombosis and graft ischemia
Antibody-mediated rejection, cont’d

• Hyperacute rejection
  ...a special form of Ab-mediated rejection
  ...pre-formed anti-donor antibodies
  ...immediate (minutes to hours)

...Nowadays it is rare..
due to screening and cross-matching to detect anti-HLA antibodies in recipient which are directed against donor’s lymphocytes
Rejection of renal transplants

• Hyperacute, acute, or chronic

• **Hyperacute**
  ...detected by the surgeon just after vascular anastomosis
  ...widespread acute arteritis and arteriolitis, vessel thrombosis, and ischemic necrosis
Rejection of renal transplants, cont’d

• Acute
  ...within days to weeks...may occur after months or even years
  ...cellular or humoral

- within the first months
- tubular and vascular lymphocytic infiltrate (CD4+ & CD8+)
- important to recognize by biopsy because it responds very well to increased immunosuppressive therapy

one of them may predominate or occur together

mainly vascular

= rejection vasculitis
...C4d is used for its detection
Rejection of renal transplants, cont’d

• Chronic

...mainly T cell-mediated

...months to years after transplantation

...interstitial fibrosis, tubular atrophy and chronic vascular changes

...much less response to immunosuppression
Improving graft survival

• Matching

• With immunosuppressive drugs, we may not need matching especially for urgent cases

• Cyclosporine
• FK506
• Mofetil mycophenolate (MMF)
• Rapamycin
• Azathioprine
• Corticosteroids
• Antilymphocyte globulin
• Monoclonal antibodies (e.g., monoclonal anti-CD3)

How can we avoid unwanted effects of immunosuppressive drugs???
Transplantation of hematopoietic stem cells

**Uses:**

- Hematopoietic malignancies
- Some nonhematopoietic malignancies
- Aplastic anemias
- Certain inherited disorders, particularly immune deficiency states and severe forms of thalassemia
Transplantation of hematopoietic stem cells, cont’d

• Ways of transfer???

• Two main problems:
  - Graft-Versus-Host disease (GVHD)
  - Immune deficiencies
Graft-Versus-Host disease (GVHD)

• Immunologically competent T cells (or their precursors) from donor

• The recipient is immunocompromised

• Mostly in HSC transplantation
  ...also solid organs rich in lymphoid cells (e.g., liver)

• Donor CD4+ & CD8+ T cells attack recipient’s tissues
GVHD, cont’d

• Acute GVHD:
  ...days to weeks
  ...epithelial cell necrosis mainly in:  -liver
  -skin
  -gut

• Chronic GVHD:
  ...after acute GVHD or insidious from the beginning
  ...skin lesions resembling systemic sclerosis
  ...manifestations resembling autoimmune diseases
GVHD, cont’d

• Can be minimized by HLA matching

• Can we manipulate donor T cells???
Thank You