» Summary - lecture 3-23-16

» Tissue and organ transplantation elicit an immune reaction in the host (in allogeneic combinations) = rejection (or host versus graft)
 » Immune response is caused by differences in MHC HLA class I and II haplotypes
 » Host versus graft response is typically T-cell mediated. Antibody anti-HLA can develop in organ/tissue recipients.
Graft versus Host

Donor lymphocytes react against the antigens of the host
Blood type matching
Blood typing test

Blood type: unknown

Blood transfusion match

www.nobelprize.org/educational/medicine/bloodtypinggame/
Hyperacute rejection

- Incompatible blood transfusions
- Donor - recipient from different species
- Mechanisms: natural antibodies reacting against specific epitopes eg,: carbohydrates
Humoral immunity

Neonatal exposed to autologous plasma

Neonatal islets exposed to human plasma

Green = viable cells

Red = dead cells
Steps in the hyperacute rejection of kidney graft

1. Pre-existing host antibodies are carried to the kidney graft.

2. Antibodies bind to antigens of renal capillaries and activate complement (C).
   - Capillary endothelial walls

3. Complement split products attract neutrophils, which release lytic enzymes.
   - Enzymes

4. Neutrophil lytic enzymes destroy endothelial cells; platelets adhere to injured tissue, causing vascular blockage.
   - Platelets
Hyperacute rejection of pig kidney (1hr hour after tx)

Courtesy Dr. DKC Cooper University of Pittsburgh
Methods to monitor rejection

**In vitro**
- MLR
- ELIspot

**In vivo**
- Biopsies
- Magnetic resonance imaging

**Graft function**
Graft function

↑ Creatinine in kidney transplants

↑ Blood glucose in pancreas/islet transplants

↓ Albumin, coagulation factors in liver transplants
In vitro

- MLR (Mixed Lymphocytes Reaction) not specific
- ELIspot (ELISA measurements of INF-gamma) highly specific
In vivo

• Biopsies
  Sampling inaccuracy - invasive

• Magnetic Resonance Imaging (iron particles)
  Sampling accuracy - non invasive
Ferrous particles (smaller than cells) injection/labeling MRI

- Particles will be up-taken mainly by Macrophages (at the transplant site) and visualized by MRI

- Cells of interest (T cells or graft in cell transplantation) can be labeled with particles and visualized by MRI
Figure 1. MR images showing effect of infusion of dextran-coated USPIO particles (3 mg Fe/kg body wt) in an allotransplant.

Shinichi Kanno et al. Circulation. 2001;104:934-938
Modulation of immuno-rejection

Immunosuppressive therapy-
combination of pharmaceutical drugs

- Generalized immunosuppression (1st generation)

- Specific immunosuppression (2nd generation)
Signal 1
Antigen/TCR

APC

Signal 2
Costimulation

CTLA4-Ig
Anti-CD40L

Anti-CD3
Anti-CD52

Anti-CD25

Anti-CD40L

Signal 3
Cytokine trigger

Cytokines

cyclosporine

tacrolimus

rapamycin

corticosteroids

Anti-IL8/IL6

Anti-TNFalpha

Cytokines

mycophenolate

azathioprine

Anti-CD25
Drawbacks of systemic immunosuppression

- Life-long therapy
- Infections
- Cancer
- Nephrotoxicity
- Antigenicity
The Edmonton Protocol for islet transplantation

Daclizumab anti-CD25 (IL-2R-alpha) antibody

Tacrolimus and sirolimus

No steroids (diabetogenic effects)
Type 1 Diabetics who were still Insulin-Free 1 Year after Islet Transplantation.
Results are shown in three eras: 1990-1993; 1994-1997; 1998-1999

- 1990-1993 (n=82)
- 1994-1997 (n=118)
- 1998-2000 (n=37)

EDMONTON
Future

- To avoid pharmacological immunosuppression
- Donor specific immune tolerance