Transplantation
MCB150
Beatty

Grafts
A graft is a transfer of tissue.

◆ **Autograft** is a graft on same animal.
◆ **Isograft** is a tissue transfer between genetically identical animals -- human twins or inbred mice of same strain.
◆ **Allograft** is graft between genetically different members of same species.
◆ **Xenograft** is a graft between different species.

Mouse Experiments
Graft rejection
◆ Rejection is initiated by adaptive immunity causing inflammation and necrosis leading to death of tissue.

Mouse Experiments
First-set rejection
Transplanted skin from incorrect MHC haplotype (allograft) is rejected in 11-15 days.
Second-set rejection
Rejection is quicker because of the presence of alloreactive memory T cells.

Human Transplantation

- Most human transplants are allografts.
- Rejection, defined clinically, is a result of alloreactive immune response.
- Challenge is to control alloimmune responses with drugs.

Human Transplantation

- Solid Organ transplant (kidney, liver, heart).
- Acute rejection: 10% of organs rejected.
- Chronic rejection: 5% of kidney and heart are lost yearly.
Types of Clinical Rejection

- **Hyperacute rejection.** Pre-existing abs.
  - Immediate inflammation from antibody binding and C' activation resulting in tissue destruction.
- **Acute Rejection.** Abs/Th cell mediated.
  - Immune response generated soon after transplant causes death of graft in first few weeks.
- **Chronic rejection.** CD4 and CD8 T cell mediated.
  - T cells cause rejection months-years after transplant.

Immune Mechanisms of Graft Rejection

**Chronic rejection**

**T cell Mediated**

- Activated CD4+ T_h1 cells initiate DTH response with macrophages
  - Damage by cytokines IFN-γ, TNF-α, LT-α (TNF-β). All cause inflammation.
- **CTL lysis of grafted tissue.**
  Most of this is from Alloreactivity
  TCR is recognizing and responding to foreign MHC molecules.

Antibody Mediated Rejection (hyperacute rejection)

- Pre-existing antibodies to blood group antigens and foreign MHC.
  - Antibodies are activating complement and clotting cascades, thus cutting off the blood supply to the graft.
Antigen Specific T cell clones can also be Alloreactive

<table>
<thead>
<tr>
<th>Normal ag specificity</th>
<th>Alloreactivity</th>
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<tbody>
<tr>
<td>OVA ( A^k )</td>
<td>( A^b, A^v )</td>
</tr>
<tr>
<td>Myoglobin ( H-2^k )</td>
<td>( H-2^b )</td>
</tr>
<tr>
<td>DNP-OVA ( A^a )</td>
<td>( A^s )</td>
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T cell mediated mechanisms of graft rejection

Minor-histocompatibility antigens

Heart Transplant Mouse Model

MHC mismatched rejected in 10 days.
MHC matched but Minor-HC mismatched non-identical inbred mice
30% still rejected only 70% acceptance after 100 days.
Prevention of Graft Rejection

Tissue Typing

◆ Serological typing is used to identify which MHC antigens are expressed by both donor and recipient.
  – Matching at both MHC Class II and Class I loci is preferred.
  – Class II antigens can directly stimulate CD4+ T cells, and are therefore of major importance in sensitizing the host to graft antigens.

How important is MHC Matching?

HLA-DR and HLA- A, HLA-B most imp to match.

Even transplants mismatched at a class I and class II locus are still 50% successful.

Tissue Typing Assays

Microcytotoxicity assay

Donor and recipient cells tested with abs against MHC molecules.
  ◆ C' is added and cell lysis is measured.
  ◆ Requires antisera to different HLA types (anti-DR3, anti-DR4, anti-A2, etc).
  ◆ Can be done in hours.

Tissue Typing Assays

Flow cytometry

◆ MAbs to different MHC alleles to identify what MHC alleles are expressed by host and which by donor.
  – Very specific.
  – Takes a few hours.
**Tissue Typing Assays**

**Mixed lymphocyte reaction**

Incubate host blood cells with irradiated donor blood cells.

- Only functional assay to measure alloreactivity.
- Most sensitive but takes 5-7 days to complete.

**Preventing Rejection**

**Immunosuppressive Therapy**

Cyclosporin A and FK506 inhibit T cell activation. These drugs bind to specific target proteins to prevent activation of calcineurin and NF-AT.

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**Side Effects**

**From Immunosuppressive Drugs**

- Increased susceptibility to infections.
  - Herpesviruses e.g. EBV, HSV, CMV.
  - Fungal infections e.g. Aspergillus, cryptococcus.
- Increased risk for virus associated cancers.
  - E.g. EBV lymphomas, Kaposi's sarcoma, and kidney carcinomas.

**Immunosuppressive Therapy**

Given after transplant and during rejection episodes

- anti-CD3 ------- Kills all T cells.
- Steroids used as anti-inflammatories.
- Cytotoxic drugs such as azathioprine and cyclophosphamide inhibit proliferation of activated cells.
New Strategies to Reduce Rejection or Induce Tolerance

◆ T cell costimulatory blockade.
  – Block CD28, block CD40.
  – Add CTLA-4 Ig fusion protein.
  (Usually in conjunction with current immunosuppressive drugs)
◆ Mixed allogeneic chimerism
  – Transfer bone marrow cells along with transplant.