Immunologic Basis of Graft Rejection

The Behavior and Fate of Skin Autografts and Skin Homografts in Rabbits
(A report to the War Wounds Committee of the Medical Research Council)
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University of Oxford

- Inducibility
- Memory
- Specificity

First Set Rejection

Rejection 7-8 Days
Second Set Rejection (Memory)

First Graft

Rejection 3-4 Days
Specificity

(b) First-set rejection
Grafted epidermis

Days 3–7: Revascularization

Days 7–10: Cellular infiltration

Days 10–14: Thrombosis and necrosis

Necrotic tissue
Blood clots
Damaged blood vessels

Specificity

Rejection 3-4 Days

Rejection 7-8 Days

“Third Party” Graft
**Terminology**

**Autograft** - One site to another on the same individual

**Isograft** - Between two genetically identical individuals
Terminology (cont.)

Allograft - between genetically distinct individuals of the same species

Xenograft - between different species

Beginning of Rejection
Rejected Mouse Skin Graft

Rejection is mediated by T cells
Role of CD4 and CD8 Cells

Laws of Transplantation

- Tx between individuals of the same inbred strain will succeed.
- Tx between inbred strains are rejected.
- Tx parent to F1 will succeed, but the reverse will fail.
The Human MHC

(a) Mating of inbred mouse strains with different MHC haplotypes

Homologous chromosomes with MHC loci

H-2<sup>b</sup> parent

H-2<sup>k</sup> parent

F<sub>1</sub> progeny (H-2<sup>b/k</sup>)
(a) HLA-A allele 2  
Donor cell  
Antibody to HLA-A allele 2  
Complement  
Cells become leaky  
Dye (trypan blue or eosin Y)  
Dye taken up

HLA-A allele 1  
Recipient cell  
No lysis  
Dye excluded

(b) Antibody to different HLA-A antigens

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Mixed Leukocyte Reaction

- Spleen
- 2000 RADS
- Add $^3$H-Thymidine
- Determine Incorporation
- 5 Days
- 18-24 Hours

Acute Rejection

- Primary Cellular
- Massive infiltration of macrophages and lymphocytes
- Decreased graft function
- Clinically appears at >10 days post-tx and can occur anytime thereafter.
Acute Rejection – Grade 1a

Acute Rejection - Grade 3a
Chronic Rejection

- Slow steady decline of graft function and progressive occlusion of vessels/passageways.
- Result of cellular and humoral mechanisms
Hyperacute Rejection

Capillary Endothelial Walls

1. Ab bind to capillaries and activate complement (C)
2. Complement Lysis and chemotaxis of neutrophils
3. Destruction of Endothelial cells
4. Blockage of capillaries and leakage of vessel contents

Donor kidney

Sensitization
- Passenger leukocyte

Class II MHC antigen

CTL

Lymph node

IL-2

T helper (TH)

T helper (TH)

T helper (TH)

Effector
Immunologic Privilege

- Eye, Testis, and Brain.
  - Anterior Chamber
  - Vitreous Cavity
  - Subretinal Space
  - Corneal Stroma

Immunologic Privilege - The Eye

- Successful orthotopic corneal allografts, intraocular retinal cell and tissue transplants.
- Unfortunate success of progressive intraocular tumors.
- Inflammation - leads to blindness, a powerful selective force.
Immune Privilege: The Anterior Chamber of the Eye

- No lymph drainage
- Cell access to eye is limited
- Only 0.01% plasma proteins
- Aqueous humor inhibits T cells, cytokine production, cell differentiation.
- APC function altered by ocular microenvironment

Immunologic Privilege - The Eye

- An Active Process
- ACAID: Anterior chamber associated immune deviation.
  - Extremely long lasting - >6 months.
  - Dominant - Can suppress even when animal is pre-sensitized.
  - Demonstrated in mice, rats, and primates.
Dental Issues and Transplantation

- Selected Side Effects of Cyclosporine
  - Gingival Hyperplasia
  - Infection
  - Nephrotoxicity
  - Hypertension
  - Tremors, Nightmares, Insomnia
  - Hirsutism
  - Fibrous Breast Tissue

Infections

- Prophylactic Antibiotics for procedures with potential to cause bacteremia.

- Metabolism of some drugs may be altered, especially for liver transplant patients (e.g. acetaminophen, lidocain, procain ampicillin etc).
Gingival Hyperplasia

- Most of overgrowth in 1st six months.
- Directly related to cyclosporine conc.
- Can be corrected surgically
- Predisposed by plaque
  - Strict oral hygiene to prevent gingivitis and other pathologies.

![Cyclosporin Induced Gingival Hyperplasia](From: ML Somcarrera et al. 1994. J. Peridontol 65:671)
## Gingival Hyperplasia in Tx Patients Receiving Cyclosporin

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## Clinical Transplantation
Objectives of Immunosuppression

- Facilitate acceptance of the allograft
  - Specific
  - Low toxicity

Basic Strategies of Immunosuppression

- High dose initial immunospression
  - Facilitate graft acceptance
  - Minimize early rejection
  - Favor induction of tolerance
- Maintenance therapy for chronic acceptance
- Augmentation to reverse acute rejection.
Major Immunosuppressants

- Cyclosporine A
- Tacrolimus (FK-506)
- Sirolimus (Rapamycin)
- Steroids
- Azathioprine
- Mycophenylate Mofetil