Immunology of Transplantation

03-390 Molecular and Cellular Immunology - Gordon Rule, PhD

Principles, Definitions and Mechanisms (part 1)

Interventions to monitor and modulate immunity in transplantation (part 2)

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Organ and tissue transplantation

- Which organs and tissues can be transplanted?

- Corneas
- Heart
- Liver
- Bone marrow
- Skin
- Blood
- Pancreas Islets
- Kidney
- Intestine
Milestones in organ transplantation

- 1954 First living donor kidney transplantation
- 1956 First bone marrow transplantation
- 1967 First successful liver transplantation
- 1967 First successful heart transplantation
Donor (Graft)/Recipient (Host) combinations

- Autologous (self)
- Iso or syngeneic (same, equal)
- Allogeneic (other, else)
- Xenogeneic (foreign, alien)
Immune response of the recipient (host) versus donor tissue (graft) = rejection (allogeneic and xenogeneic combinations)

The host recognizes the graft as “non-self” and reacts against it.

Differences in MHC (Major Histocompatibility Complex) class I and II haplotypes between donor and recipient are the basis for graft rejection (host versus graft)
<table>
<thead>
<tr>
<th>Locus</th>
<th>Alleles</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>309</td>
</tr>
<tr>
<td>C</td>
<td>167</td>
</tr>
<tr>
<td>B</td>
<td>563</td>
</tr>
<tr>
<td>DR</td>
<td>3 α and 439 β</td>
</tr>
<tr>
<td>DQ</td>
<td>25 α and 56 β</td>
</tr>
<tr>
<td>DP</td>
<td>20 α and 107 β</td>
</tr>
</tbody>
</table>
Types of immune rejection

<table>
<thead>
<tr>
<th>Type</th>
<th>Duration</th>
<th>Mechanism</th>
<th>Rejection Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACUTE</td>
<td>Several days</td>
<td>Activation of lymphocytes Adaptive immunity</td>
<td>Allotransplantation rejection</td>
</tr>
<tr>
<td>CHRONIC</td>
<td>Months to years</td>
<td>Multiple immune mechanisms Adaptive immunity</td>
<td>Allotransplantation rejection</td>
</tr>
<tr>
<td>HYPERACUTE</td>
<td>Minutes</td>
<td>Pre-existing antibodies Humoral/innate immunity</td>
<td>Blood mismatched transfusion Xenotransplantation</td>
</tr>
</tbody>
</table>
How to determine HLA haplotypes
Serological method = historical - indirect

<table>
<thead>
<tr>
<th>Antibody to different HLA-A antigens</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recipient</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Donor 3</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

If anti-HLA antibodies 1,2,3,4,5,6 bind to MHC molecules on recipient lymphocytes, complement is activated and lymphocytes killed (Trypan blue positive)

Lymphocytes

Add 1 μl T or B cells

One hour
Room temperature

Staining + fixation

Result observation and report
## HLA matching

<table>
<thead>
<tr>
<th></th>
<th>Donor</th>
<th>Recipient 1</th>
<th>Recipient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td>⭐️</td>
<td>□</td>
<td>□</td>
</tr>
<tr>
<td>HLA-B</td>
<td>◆</td>
<td>●</td>
<td>◆</td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>□️</td>
<td>△</td>
<td>□️</td>
</tr>
</tbody>
</table>

What is the best match?
**Mixed Lymphocyte Reaction**

- Recipient lymphocytes are **Responders**
- Donor lymphocytes are **Stimulators** (these cells are irradiated so they cannot proliferate)

- Mix of **Responders** + **Stimulators** (co-culture)
- Addition of 3H-labelled Thymidin (that is incorporated into new strands of DNA during cell proliferation)

- Readout: radioactivity
MLR - principle

Stimulators
Donor

Responders - Recipient
Cell-mediated rejection
Effector phase=target cell destruction
Acute allogeneic rejection - Islet graft 2wks post-transplant

Syngeneic islet graft 2wks post-transplant
Acute rejection
  Cell-mediated

Humoral acute rejection
  Anti-HLA antibody-mediated
  (it may occur more rapidly than acute rejection)

Cross-match testing
In a second transplant, what is the best match?

<table>
<thead>
<tr>
<th></th>
<th>Recipient</th>
<th>Donor 1st graft</th>
<th>Donor A</th>
<th>Donor B</th>
<th>Donor C</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HLA-B</td>
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</table>
Graft versus Host

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

Blood type: unknown

Blood transfusion match

Abs anti-A  Abs anti-B  Abs anti-Rh

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

- Incompatible blood transfusions

- Donor - recipient from two different species (discordant)

- Mechanisms: pre-formed antibody reacting against specific epitopes on the recipient cells, 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 kidney graft.

2. Antibodies bind to antigens of renal capillaries and activate complement (C^−).

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

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

Courtesy Dr. DKC Cooper University of Pittsburgh
Monitoring of graft function/rejection
Strategies to overcome immune rejection