The MHC and Transplantation

Brendan Clark

*Transplant Immunology, St James’s University Hospital, Leeds, UK*
Blood Groups


• Normal individuals have naturally occurring anti-A or anti-B isoagglutinins

• Poor outcome of transplants performed between blood group incompatible individuals.
Discovery of the MHC

- Peter Alfred Gorer (1907-1961)
- Tumour transplantation between mouse strains.
- Sarcoma tissue from Strong’s Albino A strain grew in F2 cross and backcross generations between the A strain and the resistant C57 Black strain.
- All susceptible animals possessed an antigen derived from their albino ancestors ‘antigen II’.
- Anti-antigen II antibody produced in C57 Black mice by transfer of sarcoma tissue from the A strain.
- Maximal titres of anti-antigen II antibody corresponded with time of complete tumour regression.
- ‘…genes govern the transplantibility of the tumour [and] determine isoantigenic differences’
The MHC- From Bench to Bedside

- Sir Peter Medawar (1915 -1987)
- Skin allograft rejection in burns victims

Rabbit skin graft model

<table>
<thead>
<tr>
<th>Recipient strain</th>
<th>Donor strain</th>
<th>Graft loss</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>10-14 days</td>
<td>1st set response</td>
</tr>
<tr>
<td>X'</td>
<td>Y</td>
<td>5-7 days</td>
<td>2nd set response</td>
</tr>
<tr>
<td>X'</td>
<td>Z</td>
<td>10-14 days</td>
<td>1st set response</td>
</tr>
</tbody>
</table>
The MHC – Basics

- Set of genes found in all vertebrate species
- Important role in immune function, disease susceptibility and reproductive success.
- Proteins encoded by the MHC are expressed at the cell surface and function to present ‘self’ and ‘nonself’ antigens for inspection by T cell antigen receptors.
- 50,000 – 100,000 MHC molecules on the average mammalian cell.
- Highly polymorphic.
- Role in histocompatibility, major influence on graft survival.
The Human MHC

- 6p21.3
- 3.6Mbp
- aka ‘the HLA complex’
- Divided into three regions, class I, II and III.
  - class I region encodes HLA-A, B, C (‘classical’) antigens
  - class II region encodes HLA-DR, DQ, DP antigens
  - class III region encodes HSP70, TNF, C4A, C4B, C2, BF, CYP21
- Class I genes ~3-6kb
- Class II genes ~4-11kb
MHC Antigens

aka: Human Leucocyte Antigens (HLA)

Class I antigens (HLA-A, B, Cw) found on all nucleated cells

Class II antigens (HLA-DR, DQ, DP) primarily expressed on B lymphocytes but expression can be induced on T lymphocytes and other cells
Membrane bound glycoproteins

HLA CI A,B,C molecules composed of MHC encoded 45kd heavy chain non-covalently associated with non-polymorphic \( B2 \) microglobulin

HLA CII DR, DQ, DP molecules composed of MHC encoded 31-34 kd associated a chain non-covalently associated with 26-29 kd \( B \) chain
Inheritance

- Mendelian inheritance (1:4, 1:2, 1:4)

- En-bloc from each parental chromosome (HLA-A, B, Cw, DR, DQ, DP). Each individual inherits two antigens at a given locus.

- Codominant expression. All of the inherited antigens are displayed on the cell surface (HLA phenotype).
HLA Polymorphism

- MHC is highly polymorphic
- Large number of allelic variants at each locus
- Allelic variation maintained at population level due to survival advantage
- Significant in terms of capacity of individual to mount an immune response in response to an antigenic challenge
<table>
<thead>
<tr>
<th>Gene Locus</th>
<th>Number of alleles reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-A</td>
<td>2579</td>
</tr>
<tr>
<td>HLA-B</td>
<td>3285</td>
</tr>
<tr>
<td>HLA-C</td>
<td>2133</td>
</tr>
<tr>
<td>HLA-DRA</td>
<td>7</td>
</tr>
<tr>
<td>HLA-DRB1</td>
<td>1411</td>
</tr>
<tr>
<td>HLA-DRB3</td>
<td>58</td>
</tr>
<tr>
<td>HLA-DRB4</td>
<td>15</td>
</tr>
<tr>
<td>HLA-DRB5</td>
<td>20</td>
</tr>
<tr>
<td>HLA-DQA1</td>
<td>51</td>
</tr>
<tr>
<td>HLA-DQB1</td>
<td>509</td>
</tr>
<tr>
<td>HLA-DPA1</td>
<td>37</td>
</tr>
<tr>
<td>HLA-DPB1</td>
<td>248</td>
</tr>
</tbody>
</table>

Allelefrequencies.net
HLA Nomenclature

HLA-A19 ('Broad')

| HLA-A29(A19) ('Split')
| [30,31,32,33,74]
| HLA-A*29:01(Allele)
| [29:02,29:03...]

[30,31,32,33,74]
HLA Matching

Serology (Broad)

HLA-A2, A9; B27, B15, DR1, DR2

Serology (Split)

HLA-A2, A23(A9); B27, B62(B15); DR1, DR15(DR2)
HLA-A2, A24(A9); B27, B63(B15); DR1, DR16(DR2)

Molecular (Low)

HLA-A*02, A*23; B*27, B*15; DRB1*01, DRB1*15
HLA-A*02, A*24; B27, B*15; DRB1*01, DRB1*16

Molecular (High)

HLA-A*02:01, A*23:01; B*27:01, B*15:01; DRB1*01:01, DRB1*15:01
HLA-A*02:02, A*23:02; B*27:02, B*15:02; DRB1*01:02, DRB1*15:02
Why do so many zero mismatched transplants fail?

Case 1. HLA-A*0220 vs HLA-A*0201
Why do so many mismatched transplants do so well?

Case 2: Single HLA Mismatch

Donor

Recipient
Single Donor Mismatch; Donor A32, recipient A1

Recipient HLA

A1

A29

B8

B57

Cw6

Cw7
Sensitisation

Any event which elicits an HLA directed immune response

- Pregnancy
- Blood transfusion
- Transplantation

- Serum screening
- Crossmatching
How can we explain sensitisation patterns induced by a given mismatch?

Case 3

Recipient: HLA-A*03, A*32; B*18, B*40; DRB1*08, DRB1*14

Donor: A*02, A*29; B*07, B*40; DRB1*13, DRB1*15
<table>
<thead>
<tr>
<th>Recipient HLA</th>
<th>Donor HLA</th>
<th>mmEp</th>
<th>Eplets</th>
</tr>
</thead>
<tbody>
<tr>
<td>A*0301</td>
<td>A*0201</td>
<td>8</td>
<td>……,62GE,65RKA,…,107W,…,113YH,127K,142MT,144TKH,151HV,…</td>
</tr>
<tr>
<td>A*3201</td>
<td>A*2901</td>
<td>2</td>
<td>9T,…,62LQ,…………….</td>
</tr>
<tr>
<td>B*4002</td>
<td>B*0702</td>
<td>4</td>
<td>……,65QIA,70AQA,…………….177DK,180E,</td>
</tr>
<tr>
<td>B*1801</td>
<td>B*4001</td>
<td>4</td>
<td>11AMQ,…………….144SQR,…………….177DT,180E,</td>
</tr>
<tr>
<td>Cw*0202</td>
<td>Cw*0702</td>
<td>0</td>
<td>…………………….</td>
</tr>
<tr>
<td>Cw*0701</td>
<td>Cw*0302</td>
<td>4</td>
<td>173K,………,34I,………,163L,219W,</td>
</tr>
</tbody>
</table>
LASER

DETECTOR
Crossmatching – State of the Art

‘The ideal crossmatch test that reliably detects all clinically relevant donor specific antibodies and excludes clinically irrelevant auto- and alloantibodies has still not been found’ (Susal & Opelz, 2007)
Summary

Polygeny

Allelic diversity

Codominant inheritance

• increase ‘risk’ for mismatch in transplantation

• provide target for allogeneic immune response