Immunology in Solid Organ Transplantation

„Selected Topics in Clinical Immunology“
02.05.19

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Klinik für Nephrologie und Hypertonie, Inselspital Bern

Reference
- Abbas AK, Lichtman AH und Pillai S: Cellular and Molecular Immunology, 8th Edition
- CTS Database, www.ctstransplant.org
- Swiss Transplant Annual Report, www.swisstransplant.ch
- Original References available upon request
Content

- Epidemiology of Solid Organ Transplantation
- Concepts of Anti-allograft Immunity
- Clinical Assessment of Allograft Immunity
- Strange Things in Solid Organ Transplantation
- Future in Solid Organ Transplantation
Epidemiology of Solid Organ Transplantation

**Warteliste**
- 148 (16) Herz
- 82 (4) Lunge
- 400 (30) Leber
- 1556 (26) Niere
- 101 (2) Pankreas
- 1 Dünn darm

**Transplantationen**
- 40 Herz
- 32 Lunge
- 143 Leber
- 360 Niere
- 19 Pankreas
- 0 Dünn darm

**Jahresbericht 2017, 17.04.18**

**2288**

**594**
Epidemiology of Solid Organ Transplantation

Nierentransplantationen und Warteliste

- Warteliste
- Transplantationen (exkl. Lebendspender)
- Lebendspender

Lebertransplantationen und Warteliste

- Warteliste
- Transplantationen (exkl. Lebendspender)
- Lebendspender

1. Daten für Jahr 2017
2. Daten für Jahr 2018
Organ Transplantation in Bern

Kidney Transplantation

Bern
- Kidney 50-60
- LDT 50%
- Liver 20-30
- Heart 10-20
- BMT -
All Transplants 1990-2016

- Kidney: n=381,675
- Heart: n=45,275
- Liver: n=88,217
- Pancreas: n=12,197
- Lung: n=17,779
- Heart-Lung: n=1,895

Graft survival (%)

Post-transplant time (years)
«Allograft Immunity for Dummies»: 6 Key Points

- Allogenic transplanation induces rejection of the graft

- A major gene complex for histocompatibility (MHC) is on chr 17 (mus) or chr 6 (human)
«Allograft Immunity for Dummies»: 6 Key Points

- HLA Genes are polymorphic…

<p>| | | | | |</p>
<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>H2 Class I</td>
<td>7 alleles</td>
<td>HLA-A</td>
<td>&gt; 800 alleles</td>
<td></td>
</tr>
<tr>
<td>H2 Class II</td>
<td>4 alleles</td>
<td>HLA-B</td>
<td>&gt; 800 alleles</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HLA-DQ</td>
<td>&gt; 400 alleles</td>
<td></td>
</tr>
</tbody>
</table>
«Allograft Immunity for Dummies»: 6 Key Points

- HLA Genes are polymorphic…

**HLA-A** > 800 alleles
**HLA-B** > 800 alleles
**HLA-DQ** > 400 alleles

<table>
<thead>
<tr>
<th>Switzerland</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>A</strong></td>
<td><strong>B</strong></td>
</tr>
<tr>
<td>A2</td>
<td>30%</td>
</tr>
<tr>
<td>A1</td>
<td>17%</td>
</tr>
<tr>
<td>A3</td>
<td>14%</td>
</tr>
<tr>
<td>A24</td>
<td>9%</td>
</tr>
<tr>
<td>A11</td>
<td>6%</td>
</tr>
<tr>
<td>75%</td>
<td>48%</td>
</tr>
<tr>
<td>B7</td>
<td>14%</td>
</tr>
<tr>
<td>B8</td>
<td>13%</td>
</tr>
<tr>
<td>B44</td>
<td>9%</td>
</tr>
<tr>
<td>B15</td>
<td>7%</td>
</tr>
<tr>
<td>B35</td>
<td>6%</td>
</tr>
</tbody>
</table>
«Allograft Immunity for Dummies»: 6 Key Points

MHC molecules are highly expressed on solid organs and immunogenic...

A Direct alloantigen recognition

- Allogeneic APC in graft
- Allogeneic MHC
- Alloreactive T cell

T cell recognizes unprocessed allogeneic MHC molecule on graft APC

B Indirect alloantigen presentation

- Allogeneic MHC
- Recipient's APCs
- Self MHC

Presentation of processed peptide of allogeneic MHC molecule bound to self MHC molecule

Uptake and processing of allogeneic MHC molecules by recipient APC

Peptide derived from allogeneic MHC molecule
«Allograft Immunity for Dummies»: 6 Key Points

... and induce effector mechanisms of anti-allograft immunity ...
«Allograft Immunity for Dummies»: 6 Key Points

Innate immunity
Tissue Responses
Monoc./Macrophages

Cellular Response
T cells
Cytokines
Chemokines

Neutrophils
Endothelial cells
Fibroblasts
Cytokines
Chemokines

Humoral Response
Complement-mediated
Cytotoxicity
AICD
Cytokines
Chemokines
«Allograft Immunity for Dummies»: 6 Key Points

Innate immunity
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Humoral Response
Complement-mediated
Cytotoxicity
AICD
Cytokines
Chemokines

Tubulitis
Infiltration
Capillaritis
Endothelialitis
Arteritis
Fibrosis
Atrophy
Past, current and future strategies to prevent graft loss.

Kidney Transplantation In Bern

![Graph showing graft survival rates from 70s to 90s with improved survival over time.](image-url)
Goals of Transplantation Immunology

- (induce tolerance towards the allograft)
- Recognize preformed Donor Specific Memory Immunity
- Match the Donor to the Recipient
- Prevent Allogenic Immunization and Memory Formation
- Block Effector Mechanisms Allograft Immunity
- Reverse Chronic Fibrotic Responses and Atrophy
Goals of Transplantation Immunology

- (induce tolerance towards the allograft)
- Match the Donor to the Recipient
- Recognise preformed Donor Specific Memory Immunity
- Inhibit naive allogen-specific Immunity
- Block Effector Mechanisms Allograft Immunity
- Reverse Chronic Fibrotic Responses and Atrophy
#1: Match the Donor to the Recipient: «Bloodgroup»

<table>
<thead>
<tr>
<th>Empfänger</th>
<th>Spender</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>AB</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Rh and other blood group factors do not matter.
#2: Match Donor and Recipient: «HLA Matching»

<table>
<thead>
<tr>
<th>Donor</th>
<th>Recipient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HLA-Klasse I:</strong></td>
<td><strong>HLA-Klasse II:</strong></td>
</tr>
<tr>
<td>A1, A11</td>
<td>A1, A31(19)</td>
</tr>
<tr>
<td>B7, B44(12)</td>
<td>B7, B60(40)</td>
</tr>
<tr>
<td>Cw2, Cw5</td>
<td>DR4/DR53</td>
</tr>
<tr>
<td></td>
<td>DQ7(3), DQ8(3)</td>
</tr>
</tbody>
</table>

4/8 matches or 4/8 mismatches
#3: Match Donor and Recipient: «HLA Matching»

Success of HLA-matching is dependent on donor pool

USA: 10’000 NTx/y 15%
CH: 300 NTx/y 2%

#3: Match Donor to Recipient: «It’s mostly, but not entirely HLA-dependent»

**HLA-Identical Renal Transplant Recipients: Immunosuppression, Long-Term Complications, and Survival**

V.R. Peddi, P. Weiskittel, J.W. Alexander, E.S. Woodle, and M.R. First

28/506 KTx from 1985-1996 in Cincinnati
- No induction therapy
- 1985-1990 Im+PDN
- 1990-1996 CsA/Lm/PDN

**Episodes of Rejection**
- Acute Rejection in 7/15 (46%) (first phase)
- Acute Rejection in 2/13 (15%) (second phase)
  (after CsA-Withdawal, even after 4 yrs)

**Maintenance IS**
- PDN-free in 61%
- 50% on monotherapy (mostly Imurek, rare CsA)

Transplantation Proceedings, 33, 3411–3413 (2001)
#4: Recognize preformed donor-specific memory

Pre-formed anti-HLA antibodies
- Previous Whole-Blood Transfusions
- Previous Transplantations
- Pregnancies
- Autoimmune Diseases
- Unknown
#4: Recognize preformed donor-specific memory

Pre-formed anti-HLA antibodies
- Previous Whole-Blood Transfusions
  - Previous Transplantations
  - Pregnancies
  - Autoimmune Diseases
  - Unknown
#4: Recognize preformed donor-specific memory

The New England Journal of Medicine

Volume 280 APRIL 5, 1990 Number 14

SIGNIFICANCE OF THE POSITIVE CROSSMATCH TEST IN KIDNEY TRANSPLANTATION*
RAMON PATEL, M.R.C.P., AND PAUL I. TERASAKI, PH.D.

<table>
<thead>
<tr>
<th>Graft Survival</th>
<th>Recipients with Antibodies</th>
<th>Recipients without Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive Crossmatch</td>
<td>No Crossmatch</td>
</tr>
<tr>
<td>Immediate failures</td>
<td>Failure within &lt;3 mo</td>
<td>24 (80.0%)</td>
</tr>
<tr>
<td>Failure after &gt;3 mo</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Survival for &lt;3 mo</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Survival after &gt;3 mo</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Totals</td>
<td>30</td>
<td>23</td>
</tr>
</tbody>
</table>

PPV 24/30: 80%
NPV 23/27: 86%
#4: Recognize preformed donor-specific memory «Luminex or Solid Phase Antigen Bead Assay»

**Pre-formed anti-HLA antibodies**
- Previous Whole-Blood Transfusions
- Previous Transplantations
- Pregnancies
  - Autoimmune Diseases
- Unknown

**Luminex Multiplex Assay**
(Solid Phase Single Antigen Beads)
#4: Recognize preformed donor-specific memory

Frequency and Determinants of Pregnancy-Induced Child-Specific Sensitization

Immunization with child (father) antigens...
#4: Recognize preformed donor-specific memory

**Recipient**  
(female, 60 J, 3 children, BG A)

<table>
<thead>
<tr>
<th>HLA-Klasse I:</th>
<th>A2, A24(9)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B7, B62(15)</td>
</tr>
<tr>
<td></td>
<td>Cw9(w3), Cw7</td>
</tr>
<tr>
<td>HLA-Klasse II:</td>
<td>DR11(5)/DR52, DR15(2)/DR51</td>
</tr>
<tr>
<td></td>
<td>DQ7(3), DQ6(1)</td>
</tr>
<tr>
<td>T-Zell X-Match:</td>
<td>negativ</td>
</tr>
<tr>
<td>B-Zell X-Match:</td>
<td>negativ</td>
</tr>
</tbody>
</table>

**Donor**  
(male, 62 J, 3 children, BG A)

<table>
<thead>
<tr>
<th>HLA-Klasse I:</th>
<th>A1, A11</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B27, B44(12)</td>
</tr>
<tr>
<td></td>
<td>Cw2, Cw5</td>
</tr>
<tr>
<td>HLA-Klasse II:</td>
<td>DR4/DR53</td>
</tr>
<tr>
<td></td>
<td>DQ7(3), DQ8(3)</td>
</tr>
</tbody>
</table>

**AK-Spezifität Klasse I**

| B44: | 15023 |
| B62: | 13768 |
| B76: | 15324 |
| A1:  | 12944 |
| A2:  | 12260 |
| B37: | 7744  |
| B13: | 6414  |
| B47: | 6261  |
| B27: | 5975  |
| B49: | 5612  |
| A32: | 5595  |
| B51: | 4267  |
| A36: | 4084  |
| B77: | 4005  |
| B58: | 3942  |
| B57: | 3918  |
| B38: | 3803  |
| B53: | 3744  |
| B63: | 2554  |

**AK-Spezifität Klasse II**

| DR4:  | 11280 |
| DR53: | 3961  |
| DR9:  | 2547  |
| DP1:  | 1401  |
| DR7:  | 1395  |
| DQ8:  | 1354  |

Blood Group compatible (A>A)  
1/8 matches (1xDQ)  
Crossmatch negativ  
pre-formed DSA
#4: Recognize preformed donor-specific memory

**Recipient**  
(female, 58j, 2 children, BG AB)

**Donor**  
(male, 62j, 2 children, BG 0)

<table>
<thead>
<tr>
<th>HLA-Klasse I</th>
<th>HLA-Klasse I</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1, A24(9)</td>
<td>A2, A3</td>
</tr>
<tr>
<td>B7, B56(22)</td>
<td>B35, B60(40)</td>
</tr>
<tr>
<td>Cw1, Cw7</td>
<td>Cw10(w3), Cw4</td>
</tr>
</tbody>
</table>

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<thead>
<tr>
<th>HLA-Klasse II</th>
<th>HLA-Klasse II</th>
</tr>
</thead>
<tbody>
<tr>
<td>DR4/DR53, DR8</td>
<td>DR7/DR53, DR9/DR53</td>
</tr>
<tr>
<td>DQ7(3), DQ4</td>
<td>DQ2, DQ9(3)</td>
</tr>
</tbody>
</table>

T-Zell X-Match: negativ  
B-Zell X-Match: negativ  

AK-Spezifität Klasse II  
DR7: 3718

Blood Group compatible (0>AB)  
0/8 matches  
Crossmatch negativ  
pre-formed DSA anti DR7
#5: «Inhibit the Naive Allogen-Specific Immunity.»

1. Signal 1: Antigen signal
2. Signal 2: Co-stimulation
3. Signal 3: Cytokines
4. Signal 4: «What we always do»
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

Biological Function

Allograft Histopathology

Allogen-specific Immune Response

Rejection-specific gene Transcripts
#6: After Transplantation: «Surveillance of anti-allogen Immunity»

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Biological Function

Kreatinin

Clinical Assessment

Allograft Histopathology

Histopathology

Immunofluorescence

Electron Microscopy

Donor-specific AB

Allogen-specific Immune Response

Rejection-specific Gene Transcripts

DNA Array

**Molecular Diagnosis of T Cell-Mediated Rejection in Human Kidney Transplant Biopsies**

**Methods**
- 403 biopsies, 8 reference samples
- 2 centers (Alberta, Chicago)
- Array with 54675 probes
- Prospectively collected, pooled analysis

**FINDING THE GENE SIGNATURE**

**Accuracy of 89%**
- Low sensitivity
- High specificity
- High NPV
Strange Things: «ABO-incompatible Kidney Transplantation»

«ABO-incompatible Transplantation» Karolinska-Protokoll

Rituximab Tac MMF PDN Immuno-Adsorption 2-6x

d-30 d-15 d-5 d0
Strange Things: Advantage of Double Organ Transplantation

![Graph showing kidney transplant survival comparison between kidney only and kidney + liver transplants. The graph indicates a higher survival rate for kidney + liver transplants with a sample size of 255 compared to kidney only transplants with a sample size of 867.]
Strange Things: «non-immunological factors in allograft survival»
Outlook

Reduced Toxicity

Belatacept (CTLA4-Ig)

Tolerance-Induction

combined BM/KT

Treatment of Chronic Lesions

Tocilizumab (sIL6R)
Eculizumab (αC5-AB)