Function of HLA Molecules and Clinical Implications

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Immunogenetics is the branch of medical research that explores the relationship between the immune system and genetics.

<table>
<thead>
<tr>
<th>Molecular Immunogenetics</th>
<th>Functional Immunogenetics</th>
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</table>
| *Structural characterization of Immune-Related Gene Polymorphism*  
  - Major Histocompatibility Complex  
  - Minor Histocompatibility Antigens  
  - Immune Response Genes  
  - Natural Killer Cell Receptors  
  - Genome-wide SNP Associations  | *Functional effects on the Immune Response in Health and Disease*  
  - Cellular and Humoral Alloreactivity  
  - Immunological Tolerance  
  - Autoimmunity  
  - Antigen Presentation  
  - Innate Immunity |
Immunogenetics – a Translational Science

- Immunology
- Genetics
- Immunogenetics
- Molecular/Functional
- Oncology
- Microbiology
- Transfusion M.
- Autoimmunity
- Transplantation

Diagram showing the relationships between Immunology, Genetics, Immunogenetics, Molecular/Functional, Oncology, Microbiology, Transfusion Medicine, Autoimmunity, and Transplantation.
Function of Classical HLA Molecules

TCR Ligation – Adaptive Immune Response (cellular/humoral)

**HLA-Restricted, Antigen-Specific**
- Infection
- Cancer
- Autoimmunity

**Alloreactive**
- Transplantation
- Pregnancy
- Transfusion
Function of Classical HLA Molecules

KIR Ligation – Innate and Adaptive Immunity (HLA Class I)

**Natural Killer Cell Inhibition**
- Missing Self
- Transplantation
- Infection (HIV)
- Cancer

**T cell Inhibition (?)**
- Fraction of KIR+ memory T cells
- Infection (HIV)
- Transplantation
- Cancer
Function of Classical HLA Molecules

Others

Non-HLA restricted Antigen Recognition
- Pharmacogenomics (Abacavir)

Signalling through HLA Molecules
- Transplantation
- Cancer
T Cell Maturation in the Thymus

Subcapsular Zone

Cortex

Medulla

Positive Selection on Cortical Epithelial Cells

Negative Selection on Medullary Epithelial or Dendritic Cells

T Lineage Committed Precursor TCR-CD3- CD4-CD8- "Double Negative"

αβ TCR+ CD3+ CD4+CD8- "Double Positive"

αβ TCR+CD3+ CD4+CD8+ "Single Positive"

Cytotoxic T Cell

γδ T Cell

Helper T Cell

Insufficient Affinity for Self-HLA

Apoptosis

Excessive Affinity for Self Peptide + HLA

Apoptosis

Chaplin J Allergy Clin Immunol 2010
T cell alloreactivity

Hemopoiesis

Bone Marrow

Thymus

Pre-immune T cell repertoire

Pathogen exposure

Memory T cells

Naïve T cells

Pool of Circulating T cells

Immune Response

Self-HLA + Exogenous peptides

Tolerance

Self-HLA + Endogenous peptides

Alloreactivity

Non self-HLA + Endogenous peptides
Mechanism of T cell allorecognition

5 different models of cross-recognition

Indirect

Direct

Conventional recognition

Proposed extremes of allorecognition

Molecular mimicry

HLA-B8 (Self)
Virus peptide

HLA-B44 (Allo)
Allopeptide

Induced fit

Differential TCR docking

Structural degeneracy

Molecular mimicry

Antigen-dependent tuning of pMHC flexibility
Hematopoietic Stem Cell Transplantation (HSCT)

- Replacement of HSC from a healthy HLA-compatible donor
- Double Curative Effect from Chemo- and Immunotherapy
- Immunotherapy by alloreactive T cells GvL but also GvHD
Graft versus Leukemia
Target residual blasts
Lower Relapse Risk

Graft versus Host
Target skin, intestine, liver
Transplant-Related Mortality

Tipping the Balance: Leukemia-specific Allopeptides?
Virus-specific T cells are alloreactive
Crossreactivity of memory T cells

45-80% of virus-specific T cell clones and lines are alloreactive!

...impact of donor CMV and EBV status on relapse?

Macedo, Am J Transpl 2009
Amir, Blood 2010
Early CMV replication protects from Relapse
Crossreactivity of memory T cells?

...independent from disease prognosis or stage!

Elmaagcli et al., Blood 2011
T Cell Alloreactivity

Ex-vivo HLA-A2 alloreactive T cell clones are peptide-specific

HLA-A2+ Patient with GvHD
- 50/50 peptide-specific T cell clones
- All recognize different peptides

Amir, Blood 2011
HSR-IME b-thalassemia project
HLA-identical HSCT

- Non-leukodepleted blood transfusions in Middle Eastern Countries
- Highly pre-sensitized patients (anti-HLA antibodies 81%)
- Platelet Refractoriness
- HLA-A,B typed dedicated platelet transfusions

Marktel et al., Ped Transplant 2010
Platelet Refractoriness

HLA antibodies are not depleted by Tx-conditioning

Marktel et al., Ped Transplant 2010

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Anti-HLA abs before 1st HSCT (n)</th>
<th>Conditioning immunosuppression</th>
<th>Time 1st–2nd HSCT (days)</th>
<th>Anti-HLA abs before 2nd HSCT (n)</th>
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</tbody>
</table>
Platelet Refractoriness

Number of HLA antibodies and platelet count increments

Marktel et al., Ped Transplant 2010
Platelet Refractoriness
Dedicated platelet transfusions improve outcome

Marktel et al., Ped Transplant 2010
• Structural and Functional Immunogenetics
  – Correlation between structural diversity and biological function
  – Role in many different clinical areas

• Adaptive Immunity: Thymic Selection of the TCR
  – Antigen Recognition versus Alloreactivity
  – In HSCT double-edged sword GvL versus GvHD
  – Leukemia-specific allopeptides could open new avenues for cellular therapies

• Innate Immunity: KIR
  – Role in HLA Class I mismatched HSCT
  – Role in other settings (SOT, Infection, Cancer) still controversial