KIR: Can Anything Be More Complex Than HLA?

C Hurley
Clinical Research Professionals
Data Management Conference
San Diego 2012

Disclosure:
- Principal investigator on NMDP customized typing contract providing KIR typing
- Principal investigator on ONR grant studying histocompatibility and donor selection
Which KIR Will I Talk About?

1) French cocktail with white wine

2) Island nation in the Pacific

3) Killer cell Immunoglobulin-like Receptors
Overview

• What are natural killer cells?
• How do NK cells identify unhealthy cells?
• What are KIR?
• Will transplanted NK cells kill recipient cells?
• Person to person differences in KIR
• KIR in donor selection
• Typing KIR for donor selection
Immune Cells Arise in Bone Marrow

Hematopoietic Stem Cells

Lymphoid lineage
- Lymphocytes
  - B cells
  - T cells
  - Natural killer (NK cells)

Myeloid lineage
- Monocytes / macrophages / DC
- Granulocyte

=White Blood Cells=

Photographs: Immunobiology Garland Science; Medicine@Yale
What Are Natural Killer Cells?

- Type of immune cell
- Part of body’s rapid response to infection (innate immune system)
- Kill tumor cells
- Kill cells infected by viruses
Let’s See--Overview

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1st--Let's Cover Another Killer Cell
T Cells Detect Altered Self

Normal Cell  HLA  Killer T Cell  HLA  Tumor / Infected Cell

Don't kill  Receptor  Kill
Unhealthy Cells Can Hide from T Cells by Turning Off HLA Expression

Normal Cell

Don’t kill

Killer T Cell

No killing

Tumor / Infected Cell
Natural Killer Cells Take Over to Detect “Missing Self”

- Normal Cell
- NK Cell
- Tumor / Infected Cell

- Inhibition of NK cell: No killing
- No inhibition of NK cell: Capable of killing

HLA
NK Cells Also Express Receptors That Detect “Danger” & Stimulate Killing
### Examples of NK Receptors

<table>
<thead>
<tr>
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<th>Act Ligand-“Danger”</th>
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<td>FcR CD16</td>
<td>antibody-antigen complex</td>
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<tr>
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<td>HLA</td>
<td>NKG2D</td>
<td>MICA (stress)</td>
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<tr>
<td>LILRB1</td>
<td>HLA</td>
<td>NKp46</td>
<td>Influenza HA</td>
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- Presence of self HLA = healthy cell
- Presence of “nonself” = unhealthy cell
Can Anything Be More Complex Than HLA?

**HLA**

**KIR**

Need right balance—loss of inhibition and gain of stimulation to kill
Summary - NK Cells

- Cells of the immune system
- Kill malignant or virally infected cells
- Backup for killer T cells
- Identify unhealthy cells using a series of inhibitory and stimulatory receptors
  - Target with self HLA is healthy
  - Target not expressing HLA is sick
  - Target expressing “danger” is sick
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**Killer Immunoglobulin-Like Receptors (KIR) Detect “Missing Self”**

Diagram showing NK cells interacting with normal and tumor-infected cells. Normal cells express self HLA, while tumor/infected cells express KIR.
## KIR vs HLA—Number of Different Kinds

<table>
<thead>
<tr>
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<th>HLA</th>
</tr>
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<tbody>
<tr>
<td>14</td>
<td>6</td>
</tr>
<tr>
<td>• KIR2DL1</td>
<td>• KIR2DS4</td>
</tr>
<tr>
<td>• KIR2DL2</td>
<td>• KIR2DS5</td>
</tr>
<tr>
<td>• KIR2DL3</td>
<td>• KIR3DL1</td>
</tr>
<tr>
<td>• KIR2DL4</td>
<td>• KIR3DL2</td>
</tr>
<tr>
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<td>• KIR3DL3</td>
</tr>
<tr>
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<td>• KIR3DS1</td>
</tr>
<tr>
<td>• KIR2DS2</td>
<td></td>
</tr>
<tr>
<td>• KIR2DS3</td>
<td></td>
</tr>
</tbody>
</table>

These KIR detect missing HLA, role of others not clear.
Naming of 14 KIR Based on Structure

KIR family (14 members)
- KIR2D (2 Ig)
  - KIR2DL long tail
  - KIR2DS short tail
  - KIR2DS1
  - KIR2DS2
- KIR3D (3 Ig)
  - KIR3DL long tail
  - KIR3DS short tail
  - KIR3DL

NK Cell
Can Anything Be More Complex Than HLA?

14 KIR, confusing names
## KIR vs HLA—Number of Alleles, Names

<table>
<thead>
<tr>
<th>KIR: 614 total</th>
<th>HLA: 6,810 total</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 2DL1*001</td>
<td>• A*01:02 (A1)</td>
</tr>
<tr>
<td>• 2DL1*002</td>
<td>• A*02:01:01:01 (A2)</td>
</tr>
<tr>
<td>• 2DL2*0010101</td>
<td>• B*15:02:01 (B75(15))</td>
</tr>
<tr>
<td>• 2DL4*00901</td>
<td>• C*01:02:01 (Cw1)</td>
</tr>
<tr>
<td>• 2DS1*001</td>
<td>• DRB1*04:15 (DR4)</td>
</tr>
<tr>
<td>• 3DL1*058</td>
<td>• DQB1*06:17 (DQ6(1))</td>
</tr>
<tr>
<td>• 3DS1*0130101</td>
<td>• DPB1*11:01:02 (??)</td>
</tr>
</tbody>
</table>

[KIR--No colons yet but soon]
Can Anything Be More Complex Than HLA?

**HLA**

Lots of alleles, names changed over time

**KIR**
What Are KIR?

• Family of 14 different receptors on surface of NK cells
• Some KIR detect loss of self HLA allowing the NK cell to kill
• Variations in KIR—alleles
  – Naming system like HLA
Let’s See--Overview

• What are natural killer cells?
• How do NK cells identify unhealthy cells?
• What are KIR?
• Will transplanted NK cells kill recipient cells?
• Person to person differences in KIR
• KIR in donor selection
• Typing KIR for donor selection
What Happens When T and NK Cells Are Transplanted into a Recipient?

Donor T Cell

Recognition of nonself HLA--GVHD

Recipient Cell

Foreign HLA

Is self HLA missing?

Donor NK Cell
To An NK Cell There Are Only Four HLA “Types”

**KIR**
- HLA-C group 1
- HLA-C group 2
- HLA-Bw4 +
- HLA-Bw4 -

**HLA**
- HLA-B
  - 1,786 variations
- HLA-C
  - 938 variations
What Happens When Natural Killer Cells Are Transplanted?

NK cell will kill if:
1. Self HLA is absent (not inhibited)
2. Stimulatory ligand is present

Bw4+ Donor NK Cell

HLA-Bw4-
Recipient Normal Cell

HLA-Bw4-
Recipient Tumor Cell

Bw4- = Bw6+
Can Anything Be More Complex Than HLA?

HLA

KIR

HLA may differ but still be self
NK Cells in Transplantation

• Donor’s NK cells
  – Don’t consider patient’s NK cells

• Missing self HLA
  – 4 types: C1g, C2g, Bw4+, Bw4-

• Stimulatory ligand
  – Differences in ability to kill disease target
    (eg AML vs ALL; tumor vs normal)
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Like HLA, KIR Genes Cluster Together on a Chromosome
Number KIR Genes on Chrom 19 Varies from 4 to 14

<table>
<thead>
<tr>
<th>KIR--7</th>
<th>KIR--9</th>
<th>HLA (9-10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3DL3</td>
<td>3DL3</td>
<td>DP A1/B1</td>
</tr>
<tr>
<td>2DL3</td>
<td>2DS2</td>
<td>DQ A1/B1</td>
</tr>
<tr>
<td>2DL1</td>
<td>2DL2</td>
<td>DR A/B1</td>
</tr>
<tr>
<td>2DL4</td>
<td>2DL4</td>
<td>[DRB3 (4,5)]</td>
</tr>
<tr>
<td>3DL1</td>
<td>3DS1</td>
<td>B</td>
</tr>
<tr>
<td>2DS4</td>
<td>2DL5</td>
<td>C</td>
</tr>
<tr>
<td>3DL2</td>
<td>2DS5</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>2DS1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3DL2</td>
<td></td>
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</table>

OR OR …
Can Anything Be More Complex Than HLA?

**HLA**

**KIR**

Number KIR genes vary among people
KIR Gene Clusters Have Names
These 5 Are Most Common in European Americans

Centromeric
• cA01  3DL3~2DL3~2DL1
• cB01  3DL3~2DS2~2DL2~2DL5~2DS3~2DL1
• cB02  3DL3~2DS2~2DL2

Telomeric
• tA01  2DL4~3DL1~2DS4~3DL2
• tB01  2DL4~3DS1~2DL5~2DS5~2DS1~3DL2

B has more S genes
Each Person Carries 2 Copies of Chromosome 19

Chromosome 19 (paternal)
- cA01  3DL3~2DL3~2DL1
- tA01  2DL4~3DL1~2DS4~3DL2

Chromosome 19 (maternal)
- cB01  3DL3~2DS2~2DL2~2DL5~2DS3~2DL1
- tA01  2DL4~3DL1~2DS4~3DL2
Can Anything Be More Complex Than HLA?

**HLA**

**KIR**

Chromosome structure matters
KIR Genes

• Not all KIR genes may be present in an individual
• Individual copies of chromosome 19 bear different sets of KIR genes
• Two clusters of KIR genes on chromosome—centromeric & telomeric
• Each individual carries 2 centromeric and 2 telomeric gene structures
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Clinical Observations Suggest Role for KIR in Transplantation

Reduce risk of relapse by:

• Selecting donor whose NK cells detect missing self HLA in the recipient
• Selecting donors whose NK cells carry CenB haplotypes

Note that not all studies support these observations
Hematopoietic Stem Cell Transplantation

Hypothesis: Donor NK Cells Will Target Tumor Cells if Self HLA Is Absent

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<th>Ligand</th>
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<tr>
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<td>HLA-C1G</td>
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Donor NK

KIR2DL3

Recip Cell

HLA-C2G

Donor NK

KIR2DL3

No inhibition

Killing

Donor NK

KIR2DL3

Inhibition

No killing

Improved Survival in AML Based on KIR CenB Presence in Donor of Hematopoietic Stem Cells

Cooley et al. Blood, 2010
Understanding Role of KIR—Reduce Risk of Relapse

• Donor characteristics
  – KIR genes / alleles
  – “Licensing” by donor HLA
• Patient characteristics
  – Disease target for stimulatory receptors
  – HLA type (KIR ligand)
• Treatment
  – Graft (presence T lymphocytes)
  – Conditioning regimen
Can Anything Be More Complex Than HLA?

**HLA**

**KIR**

Lots of factors to consider for donor selection
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What Is Typed?

• KIR for donor only
  – 14 KIR genes present or absent
  – KIR gene copy number
• HLA for donor & recipient
• Interpretation of KIR haplotypes present
  – Eg, number of centromeric B haplotypes
Can Anything Be More Complex Than HLA?

**HLA**

**KIR**

Require both HLA & KIR typing
Can Anything Be More Complex Than HLA?

**HLA**

Hard to type so many alleles

**KIR**
Use of KIR

• Select best donor to kill residual tumor
  – At transplant
  – Later through donor lymphocyte infusion
• Matching HLA should be top priority
  – Do not deliberately mismatch HLA to get NK killing
• Currently consider only within a clinical trial
KIR: Can Anything Be More Complex Than HLA? Yes!!

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More Confused?

Try this!