Modeling the evolution of NK cell receptors

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How do NK cells detect "missing-self"?

NK cell receptors

Immunoglobulin-like receptors
Lectin-like receptors

NK cell

Inhibitory
Activating

How do NK cells detect "missing-self"?

Two receptor families

NK cell receptors

Immunoglobulin-like receptors
Lectin-like receptors

NK cell

Inhibitory
Activating

Missing-self detection

NK cell receptors monitor the expression of MHC class I on the cell surface.

NK cell detects normal MHC class I expression

NK cell detects the presence of MHC and the loss of MHC class I expression

NK cell spares the healthy epithelial cell

NK cell kills the virus-infected epithelial cell

Figure 13.3: The Immune System, 3rd Ed., Gerhard Science 2009

Figure 13.2: The Immune System, 3rd Ed., Gerhard Science 2009

Figure 13.1: The Immune System, 3rd Ed., Gerhard Science 2009
Conserved receptor and conserved ligand should do the job...

- HLA-E conserved MHC-class I, which presents peptides coming from HLA-A, HLA-B, and HLA-C
- Inhibitory NKG2A binds to HLA-E
- HLA-E + NKG2A monitor the expression of the other HLA molecules
  → Conserved feature of the human immune system

But it's not that simple...

- KIRs bind to the polymorphic site of the MHC molecule
  → KIR footprint overlaps with the TCR binding site
- KIRs are specific

But it's not that simple... KIR are highly diverse

- KIRs are specific and diverse?

Strategies of viruses to escape the immune response

- Viruses evolve "MHC downregulation" to escape from the adaptive immune system
- Viruses evolve MHC decoys to escape from the NK cells
Strategies of viruses to escape the immune response

- MCMV down-regulates MHC expression
- MCMV evolved viral decoy molecules to avoid "missing - self" detection

Do viral decoys have an impact on the evolution of NK cell receptors?

Recap I

For missing-self recognition:
- A limited set of monomorphic NK cell receptors should do the job
- But KIRs are specific and highly diverse
- **Hypothesis**: viruses evolving decoys to escape the NK cell response can drive the evolution of KIR complexity

Agent-based modeling

- An agent is a persistent thing which has some state, and which interacts with other agents, mutually affecting each other’s states
  - "Agent is a thing that does things to other things"
- Rules/Events:
  - what and how they do
  - depend on the state
- Monitor the set of states
  - recognize patterns in the behavior

Agent Based Model

- Hosts:
  - simplified humans carrying a diploid genome
  - 1 MHC
  - 5 NK cell receptors
- NK education process:
  - KIR recognizing own MHC is licensed
- Initialization: genes from pre-defined pools
Agent Based Model: Events

- Birth
  - Sexual reproduction
  - Mutation

- Death
  - age (a) - and viral load (VL) dependent
    \[ \delta_{a, VL} = \delta_0 \left( \exp[\ln(0.6) - 10.5] \cdot \exp[-10.6 + 8] + V_{L_{aa}} + V_{L_{a}} \right) \]
  - \( \delta_0 \) = max death rate
  - \( V_{L_{aa}} \) = Viral load during acute infection
  - \( V_{L_{a}} \) = Viral load during chronic infection

- Infection
  - transmission upon contact with another infected host

- Immune escape
  - MHC downregulation
  - Evolution of MHC decoys

Receptor-MHC recognition: specificity scale

- Receptors and ligands represented by bit strings
- Receptor-MHC recognition: complementary match
- Specificity: length of the adjacent match (bit scale)

KIR: 01100011001100101
MHC: 11111101010011001

Infection and viral strategies

- Wild-type virus
- MHC downregulation
- MHC downregulation + viral decay:

Specificity Scale

<table>
<thead>
<tr>
<th>Specificity</th>
<th>MHC recognition</th>
<th>Located KIR</th>
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</table>

\[ n = 10(1 - p^2) \]
Table 1. Relationship between specificity and crucial parameters for clearing the infection

<table>
<thead>
<tr>
<th>Specificity</th>
<th>MHC recognition Frequency</th>
<th>Licensed KIRs Frequency</th>
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<tbody>
<tr>
<td>1</td>
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<td>9.96</td>
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<tr>
<td>10</td>
<td>0.0006</td>
<td>0.12</td>
</tr>
</tbody>
</table>

\[ n = 10(1 - (1 - p)^2) \]

KIR: 011100110011001011
MHC: 1111110110101010100

KIR: 011000110011001011
MHC: 11111100101010100

If "missing self" detection can be achieved by only one receptor....

Why are KIRs specific?
Why are KIRs diverse?

Recap II

For missing-self recognition:
- A limited set of monomorphic NK cell receptors should do the job
- But KIRs are specific and highly diverse
- Hypothesis: viruses evolving decoys to escape the NK cell response can drive the evolution of KIR complexity

To study this hypothesis:
- We use an agent-based model (collection of agents and their states, and the rules governing their interactions)
- We model viruses evolving MHC down-regulation and decoy molecules
- Compared populations which differ in their specificity of the KIR-MHC interactions
Specific KIRs are detrimental against viruses down regulating MHC expression

Specific KIRs protect against viruses evolving MHC-like molecules

Viruses evolving MHC like decoys

If "missing self" detection can be achieved by only one receptor….

Why are KIRs specific? Why are KIRs diverse?
What is the effect of specificity on the evolution of KIRs?

- Diversity evolves only in very specific systems

Recap II

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To study this hypothesis:
- We use an agent-based model
- We model viruses evolving MHC down-regulation and decoy molecules
- Compared populations which differ in their specificity of the KIR-MHC interactions

We found that:
- KIR specificity is detrimental to hosts infected with MHC downregulating viruses
  - Cross-reactive NK cell receptors evolve
- KIR specificity is protective against viruses evolving decoy
  - Specific NK cell receptor evolves
- KIR diversity evolves as a consequence of the specific interaction between them and MHC