A selective sweep in chimpanzees: Is SIV the culprit?

Some MHC lineages are old and predate speciation

The ABC of MHC

Polymorphism: Some MHC loci display variation at the population level
MHC & Disease

Mhc polymorphisms are associated with susceptibility and resistance to diseases

Any evidence for selection on the MHC

Selection
Operates on an individual

Evolution
Operates on a population and may result in differences in gene frequencies

MHC and selection:
The monomorphic MHC argument

Cheetah

Syrian hamster

Time for monkey business

"Sir, listen! There’s more! I’ve named the rule with this big ears Boss, and he is surely the nerd of the social group—a prime example if you will!"
Humans & Chimpanzees
About similarities & differences

- Nucleotide sequence similarity: 98.7%

• Insertions/deletions (indels): > 5%
Chimpanzees and AIDS: Some Facts

- Worldwide more than 150 animals (Ptv) have been infected with various HIV-1 isolates...No evidence for AIDS-like disease

- Only one report of an experimentally infected animal with AIDS-like disease (Novembre et al., J. Virol., 1997, 4086)

- Evidence for natural infections (SIVcpz) and AIDS? (Keele et al., Nature 2009, 460)
Predation and the route of SIV/HIV infections

Why are chimpanzees relatively resistant to AIDS?

Candidate resistance genes

MHC class I?

Specialization of functions
- MHC class I molecules (HLA-A, -B, and -C) bind and present antigenic peptides from intracellular origin to the receptors on CD8-positive cells resulting in the lysis of infected cells.
- MHC class II molecules (HLA-DR, -DQ and -DP) play a similar role in the presentation of peptides from extracellular origin to CD4-positive cells resulting, for instance, in the production of antibodies.

Similarities and dissimilarities at the locus level

The devil is in the details?

Initial observations part I:
Signatures of selection...the first hints

Chimpanzees versus Humans
- Chimpanzees only possess orthologues of the HLA-A1/A3/A11 family
- Seem to have a severely reduced B/C locus repertoire (lineages)
- Evidence for loss of particular class II lineages
Initial observations part II:
Further evidence for selection

Chimpanzees experienced a selective sweep affecting the MHC class I gene repertoire, approximately 2-3 myr ago, as was illustrated by intron 2 analyses. (de Groot et al., PNAS, 11748-53, 2002)

Chimpanzees have only one hybrid MIC gene, displaying limited polymorphism. (de Groot et al., Mol Biol Evol, 1375-85, 2005)

Small Tandem Repeat analysis maps strongest effect of the sweep to the Patr-B region. (de Groot et al., Mol Ecol, 2074-2078, 2008)

Hypothesis:
The MHC class I repertoire reduction in chimpanzees may have been caused by an HIV-1/SIV like retrovirus.

Preliminary studies identified conserved and shared HIV-1 epitopes

<table>
<thead>
<tr>
<th>gag epitope</th>
<th>restriction elements</th>
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<tr>
<td>HOAISPRTL</td>
<td>HLA-B<em>5701 Patr-B</em>02</td>
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<tr>
<td>KRWIILGLN</td>
<td>HLA-B<em>2705 Patr-B</em>03</td>
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Balla-Jhaghoosinng et al, J Immunol 1999, 2308

Aim of the subsequent functional studies

To investigate whether the selective sweep was possibly caused by HIV-1/SIV<sub>cpz</sub> (or a closely related ancestor) and has resulted in the preferential selection of Patr molecules that are similar to AIDS-resistant molecules in human individuals, such as HLA-B*27/B*57.
Outline of the study

• Determine peptide binding motifs. (Patr-A*0301, B*0101, B*0301, B*0501).

• Scan of the HIV-1/SIVcpz proteomes. Attention was focussed on the Gag protein.

• Selected peptides/potential epitopes were tested for actual binding to their corresponding MHC class I molecules.

• Re-evaluation of cellular immune response data of three chimpanzees of an HIV-1 infected cohort.

Chimpanzee MHC class I peptide binding motifs

Patr class I molecules target similar conserved areas of HIV-1 Gag as HLA-B*27/B*57

Evaluation of CTL data in the context of peptide binding studies
Chimpanzee founder haplotypes

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Chimpanzees' MHC class I repertoire is skewed to favor the survival of animals whose Pat molecules recognize conserved areas of Gag, a property shared with HLA-B*27/B*57.

A quantitative aspect of Ir genes

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The evolutionary rat race between hunters (pathogens) and prey (host)

The chimpanzee MHC class I repertoire is skewed to favor the survival of animals whose Pat molecules recognize conserved areas of Gag, a property shared with HLA-B*27/B*57.
What is the biological function of MHC polymorphism?

It MAY pay to be different!
The CG&R team

Thanks to all other collaborators/team members at the BPRC, LUMC and UU.

Artwork by Henk van Westbroek and Gary Larson (Farside)