Preferential loss of HIV-1 derived CTL epitopes restricted by protective HLA-B alleles during the HIV-1 epidemic

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HIV-1 and Cytotoxic T Lymphocytes

HLA class I molecules present viral peptides to CTL => dictate the repertoire of CTL responses

CTL escape mutations are transmissable
=> can be stable or revert to wild type in a recipient with a different HLA background
i) Is there evidence that current HIV-1 strains contain fewer HLA-binding epitopes than HIV-1 strains from the start of the epidemic?

ii) Is there a difference between HLA alleles that are common in the population vs. rare alleles?
Study design

Patients & methods:
12 HIV infected individuals with sc in 1985
15 HIV infected individuals with sc in 2005/06

All individuals are Subtype B infected Caucasian males, treatment naïve

Sequence data of Gag (P17, P24), Nef, Protease and RT, isolated within one year after seroconversion

Analysis of the data using peptide prediction programs for proteasomal cleavage, TAP transport and HLA binding
Decreased number of CTL epitopes presented via HLA-B alleles

- HLA-A*0101
- HLA-A*0201
- HLA-A*2402
- HLA-B*0702
- HLA-B*0801
- HLA-B*4403
- HLA-B*2705
- HLA-B*5701
Decrease in the number of CTL epitopes is caused by HLA-B*2705 and B*5701
Adaptation of HIV-1 is driven by HLA-B alleles associated with slow disease progression.
Conclusions

Even within 20 years of HIV-1 evolution, HIV-1 has significantly adapted to the human immune system by decreasing the number of CTL epitopes.

Adaptations are not driven by the most common HLA molecules in the human population, but by HLA-B molecules associated with a low relative hazard of HIV-1 disease progression.
Correlation between HIV variant frequency and HLA prevalence in study cohorts

Kawashima et al. Nature 2009
Population frequency & adaptation

- Population frequency of HLA-X
- Adaptation to HLA-X

- Population frequency of HLA-Y
- Adaptation to HLA-Y
• The HLA alleles for which we observed significant adaptation are not common in the Caucasian population

• Mutations in epitopes restricted by HLA-B27 and B57 have been shown to be associated with reduced viral fitness

=> such escape mutations are expected to revert to wildtype upon transmission to a host that does not express this allele
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All participants of the Amsterdam Cohort on HIV infection and AIDS
• HLA-A alleles with a RH<1 are: A*0201, A*0301, A*1101, A*2601, A*3101, A*3201 (not available when using NetMHC), and A*6901.

• HLA-B alleles with a RH<1 are: B*0801, B*1801, B*2705, B*4001, B*5101, B*5701 and B*5801.
• HLA-B alleles with a RH>1 are: B*0702, B*1501, B*3501, B*4403, B*4501 and B*5301.
HLA alleles grouped based on frequency

- HLA-A alleles with a frequency > 5% are: A*0101, A*0201, A*0301, A*1101 and A*2402.

- HLA-B alleles with a frequency > 5% are: B*0702, B*0801, B*1501, B*2705, B*3501, B*4001, B*4403 and B*5101.
- HLA-B alleles with a frequency < 5% are: B*1801, B*4501, B*5301, B*5701 and B*5801.
## HIV-1 polymorphisms identified by phylogenetic correction

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Escape mutations can either revert or be stable after transmission.

**HLA-B57/5801-positive subject**

1. ISW9 epitope
2. h1
3. h2
4. h3
5. h4
6. Cyclophilin A binding loop
7. TW10 epitope
8. h5
9. h6
10. h7

**HLA-B57/5801-negative subject**

1. ISW9 epitope
2. h1
3. h2
4. h3
5. h4
6. Cyclophilin A binding loop
7. TW10 epitope
8. h5
9. h6
10. h7

**Acute phase**

1. A146P
2. H219Q
3. T242N
4. G248A

**Chronic phase**

1. A146P
2. H219Q
3. T242N
4. G248A

Leslie et al. Nat Med 2004