Transmitted and intra-host CTL escape drive HIV disease progression

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Initial challenge (founder virus) → Initial CTL response → Adapting CTL response → Escaped virus

CTL escape and VL

No immune response, WT

Immune response, WT

Functional avidity
Polyfunctionality
Cytotoxicity
Breadth
Depth
Magnitude
Gag focused
CTL escape and VL

No immune response, WT

Immune response, Escaped

Immune response, WT

Abrogate HLA binding
Epitope processing
Alter TcR interaction
CTL escape and VL

No immune response, WT

No immune response, Escaped

Immune response, Escaped

Immune response, WT

Fitness costs
What is the role of *intra-host* and *transmitted* escape in disease progression?
A probabilistic model of adaptation

Training: phylogeny
Testing: Inferred best sequence in the absence of HLA pressure

Pr(s|HLA, f)
A probabilistic model of adaptation

\[
\frac{\sum_f \Pr(s|HLA, f) \Pr(f|\psi)}{\sum_f \Pr(s|0, f) \Pr(f|\psi)}
\]

\[
\text{Adapt}_{HLA}(s) = g \left( \frac{\mathcal{L}(HLA|s)}{\mathcal{L}(0|s)} \right)
\]

-1: HLA-
+1: HLA+
0: Equally likely
In words...

$\text{Adapt}_{B57}(s):$

How much more likely is the HIV sequence to be observed in a chronically infected individual whose CTL response is restricted solely by B*57, compared to an individual with NO CTL response, averaged overall all possible founder viruses.

Autologous adaptation

The average adaptation of the autologous sequence to each of the individual’s 6 HLA alleles
Data

Training
1,888 Clade B, full proteome (except gp120). Vancouver, No. America, Austr
2,066 Clade C, Gag/Pol/Nef. Durban and Bloem. So. Africa, Botswana, Zambia

Testing
Elite controllers (N=24) and matched progressors (N=80)
1,048 Clade B with VL and CD4 counts
1,877 Clade C with VL and CD4 counts
78 Linked transmission pairs with 2 years of longitudinal follow up (Zambia)
Adaptation correlates with progression

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<th>Covariate</th>
<th>p</th>
<th>Beta</th>
<th>FVE</th>
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</table>

Data from T. Miura
Adaptation correlates with progression
Allele specific adaptation
Adaptation precedes progression

Unpublished, data from E Hunter
Adaptation linked to clinical progression

What happens when escape is transmitted?
Transmitted escape

Rapid progression
Universal escape

Similar progression
Context-dependent escape

Time
Transmitted escape

Predict Viral Load

Unpublished, data from E Hunter
Transmitted escape

Escapes are “universal”

Immune system does not simply target the first challenge

Epitopes don’t bind to HLA?

T-cells can’t recognize epitopes or yield weak responses?
Adaptation to human populations

Hypothesis

Individuals for whom circulating HIV is well adapted will have higher VL

Circulating viruses define expected transmitted virus

For each individual, calculate average adaptation all of all other sequences in the cohort to their HLA alleles
Adaptation to human populations

Hypothesis

Protective HLA alleles are those for which circulating virus is not well adapted

Estimate HLA-specific VL/CD4 effects using random HLA effects

Clade C VL

\[ R^2 = 0.14 \]
\[ p = 0.001 \]

Clade B VL

\[ R^2 = 0.37 \]
\[ p = 8 \text{e-07} \]
Adaptation to human populations

Hypothesis

Protective HLA alleles are those for which circulating virus is not well adapted.

Estimate HLA-specific VL/CD4 effects using random HLA effects.
Adaptation to human populations

Hypothesis

Protective HLA alleles are those for which circulating virus is not well adapted

Estimate HLA-specific VL/CD4 effects within each country
Conclusions

Autologous escape is a key driver of disease progression
Separates elite controllers from progressors
Explains more variance in VL and CD4 than HLA-B
Predicts future changes in VL during early infection

Transmitted escape is a key driver of disease progression
Predicts early setpoint VL and CD4 decline
Population level adaptation predict chronic setpoint VL
Protective alleles are those for which the circulating virus is not well adapted

Escape mutations are universal
Our immune systems are ill-equipped to deal with many viral variants
Can vaccines change that?
Collaborators

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