Contribution of human TRIM5α in HIV-1 control in vivo

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Host antiviral defenses

Innate immunity

- Widely conserved among species
- Non-specific, no memory
- Ex : NK cells, interferon...

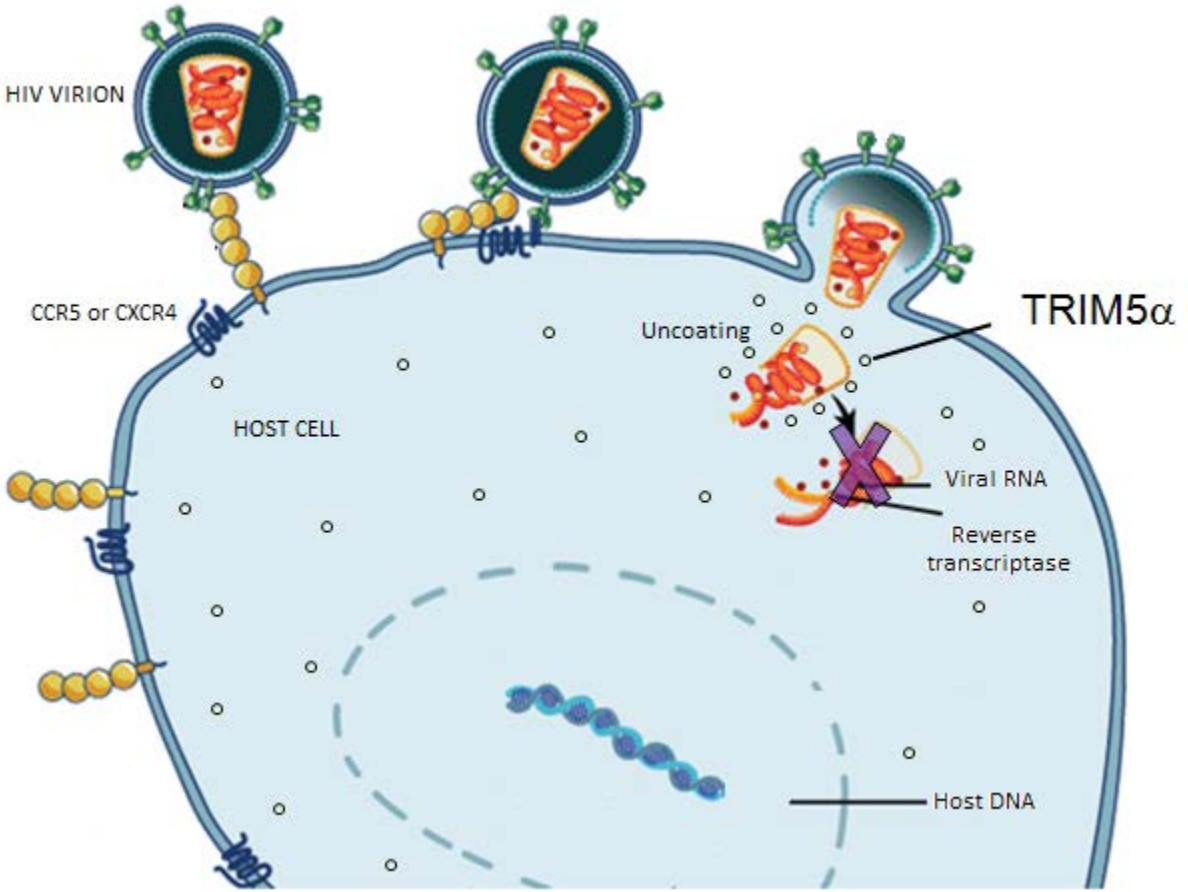
Adaptive immunity

- Fairly conserved among species
- Highly target-specific, strong memory
- Ex : antibodies, CTLs...

Intrinsic immunity

- Species-specific : selected by lethal virus infections
- Not always virus-specific
- Specific countermeasures evolved by viruses
- Ex : APOBEC3, Tetherin, SamHD1, TRIM5α

TRIM5α - a restriction factor



Adapted from www.niaid.nih.gov

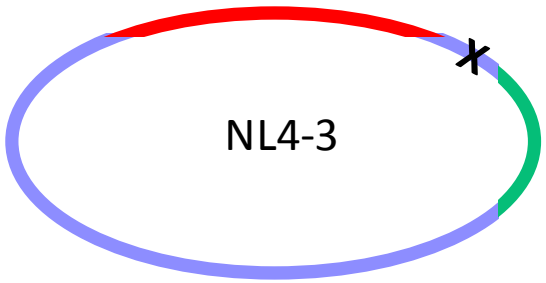
Antiviral activity of TRIM5α is species- and host-specific

- HIV-1 is particularly susceptible to TRIM5α from some primate species (macaque)
- Retroviral susceptibility to TRIM5α is determined by amino-acid variations in the capsid protein
- TRIM5α activity is determined by a variable region of the molecule, the site of strong positive selection
- Human TRIM5α has generally been found poorly active on HIV-1

Methods

Recombinant Viruses

Gag-protease from clinical isolates

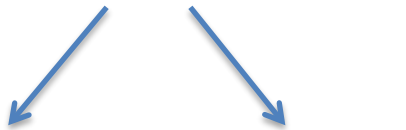


Deletion in Env

Renilla luciferase (in place of Nef)

Target cells

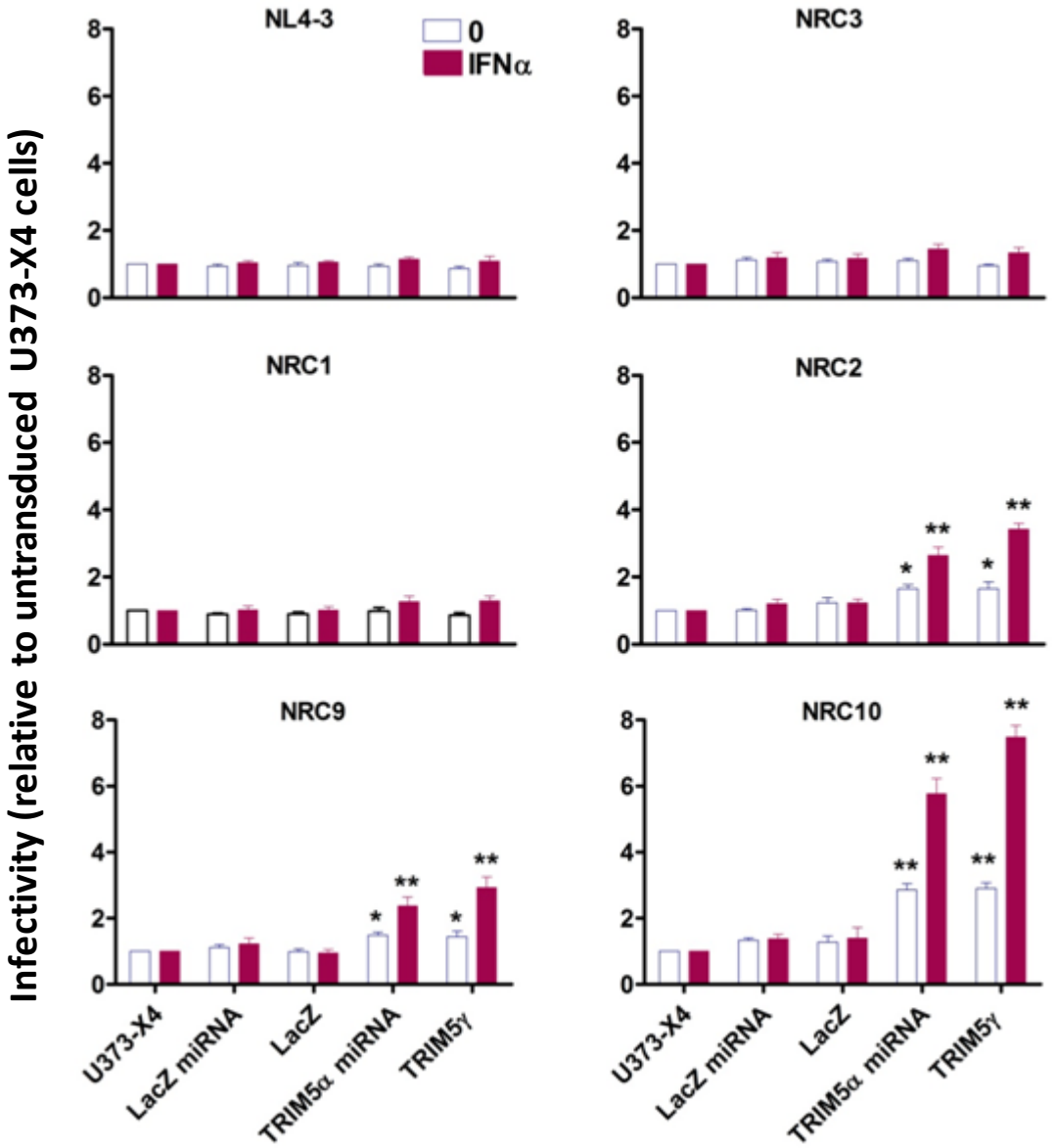
U373-X4 cells



control **TRIM5γ**

TRIM5α activity + -

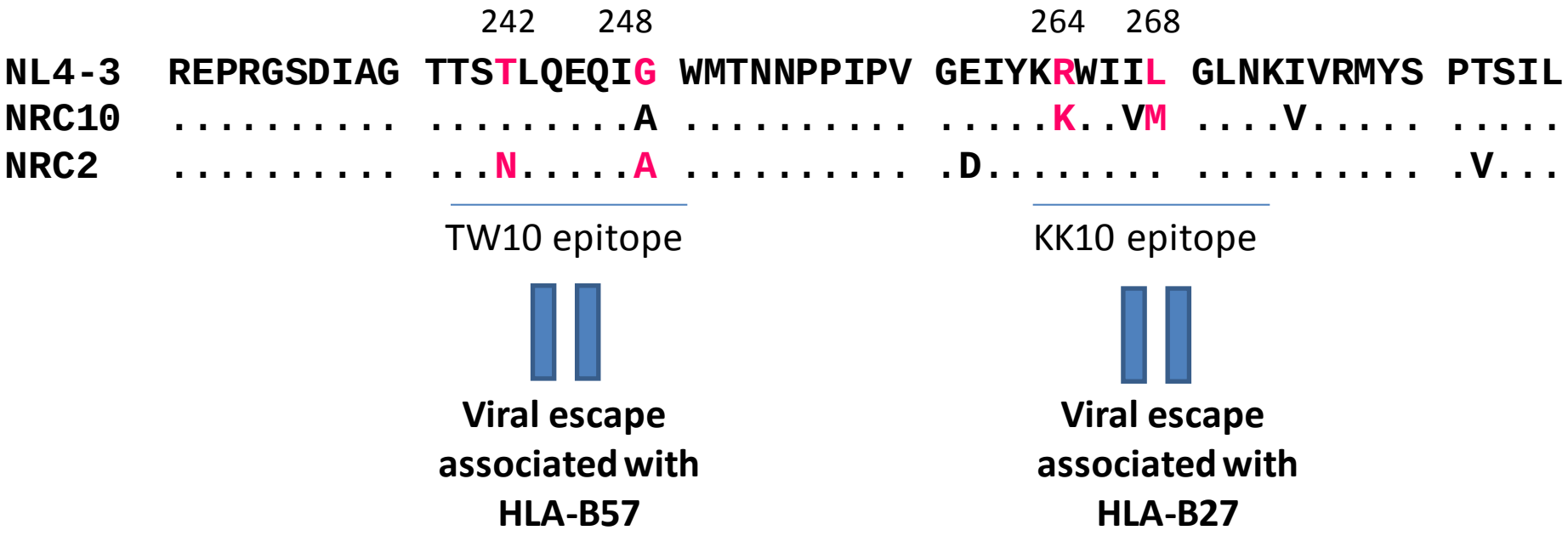
Different TRIM5α sensitivities with different HIV-1 capsid sequences



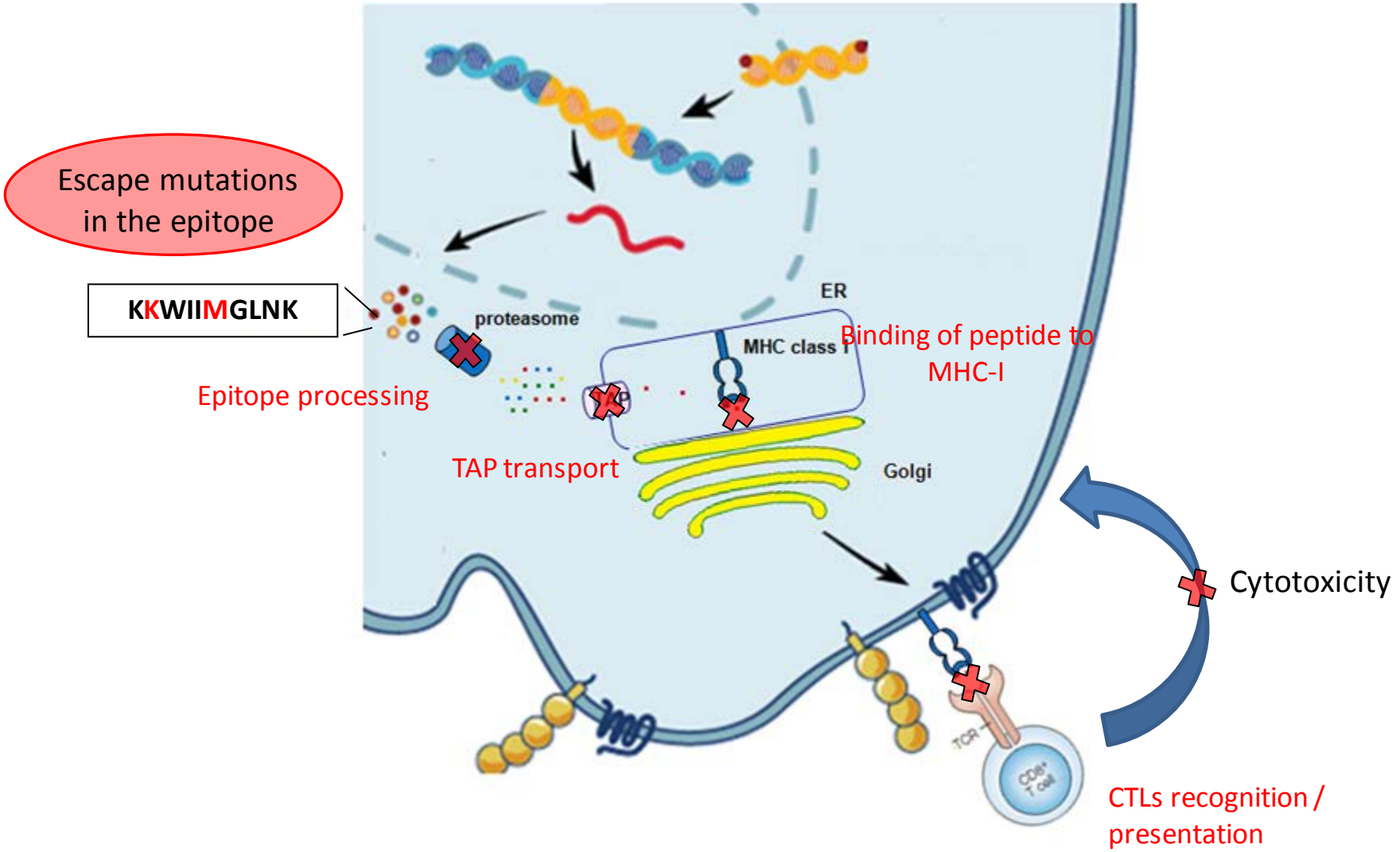
* , p<0.05
**, p<0.001

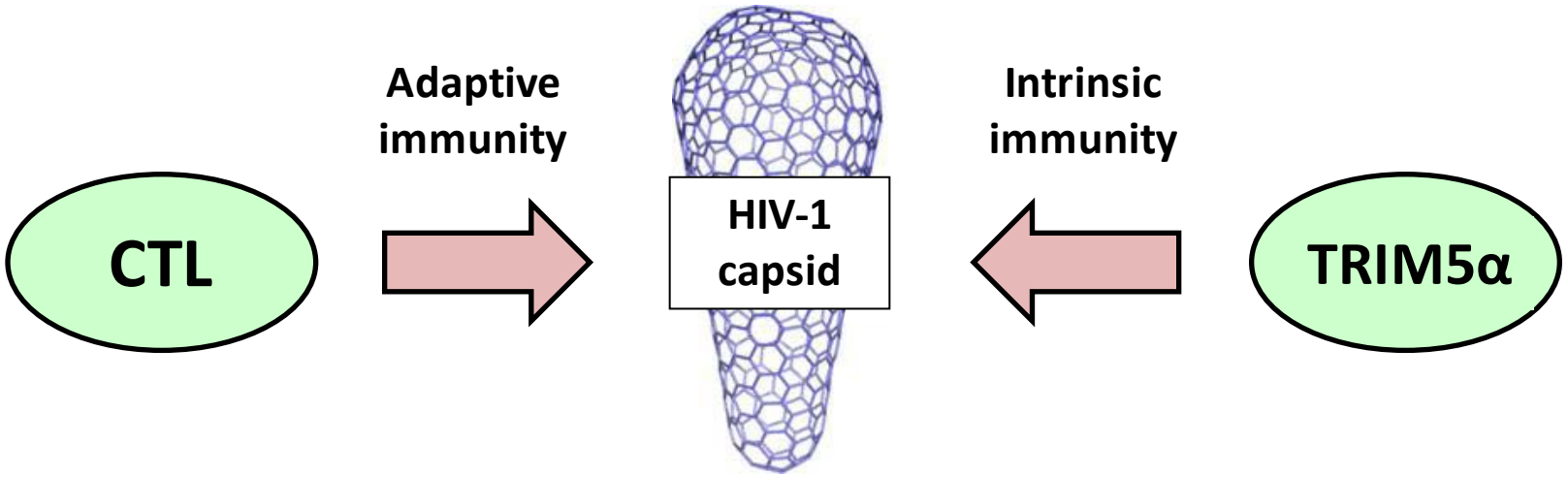
Battivelli and al, *J.Virol*, 2010

CA sequences show mutations associated with viral escape to CTLs



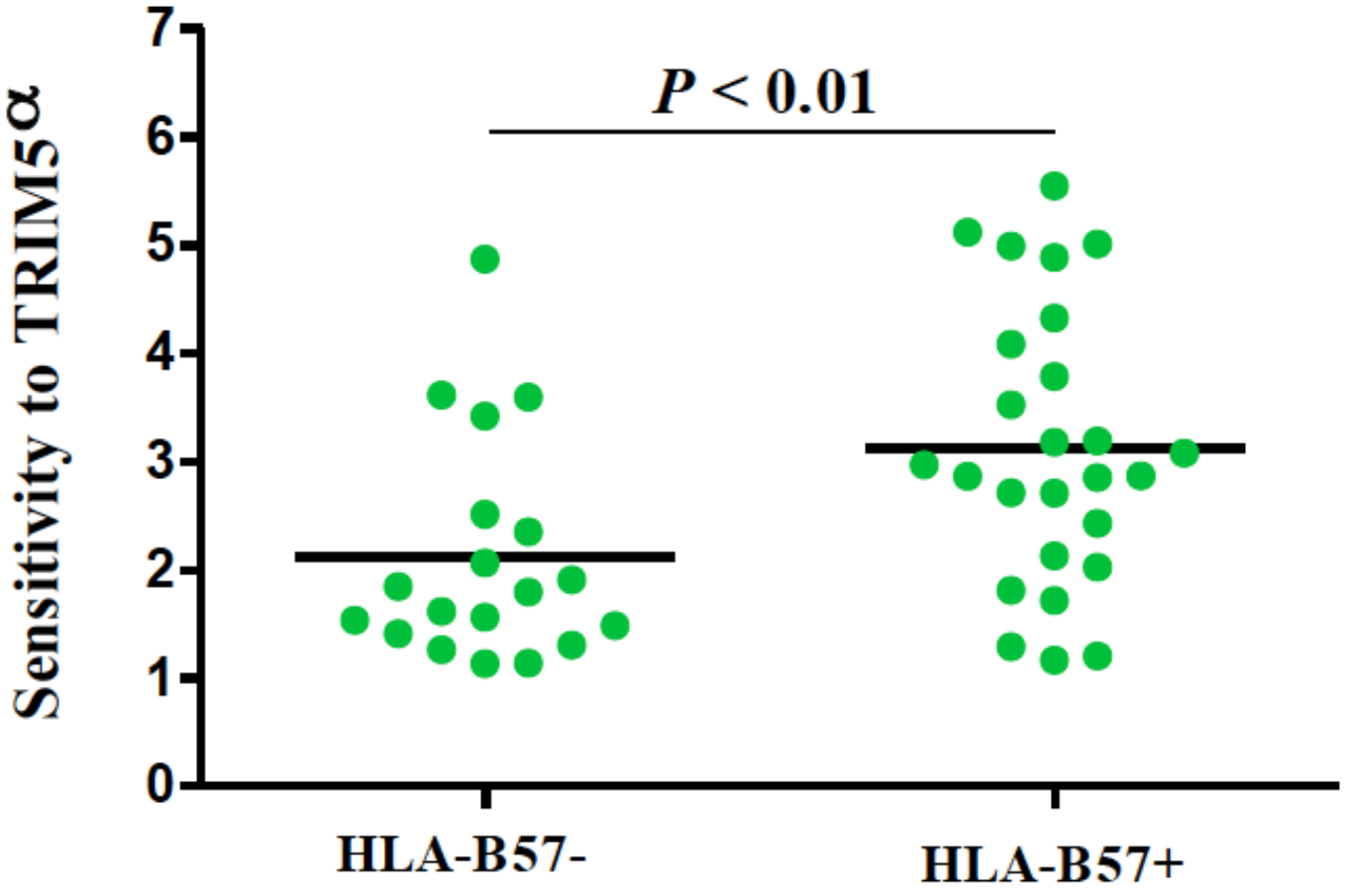
HIV CTL escape mutations



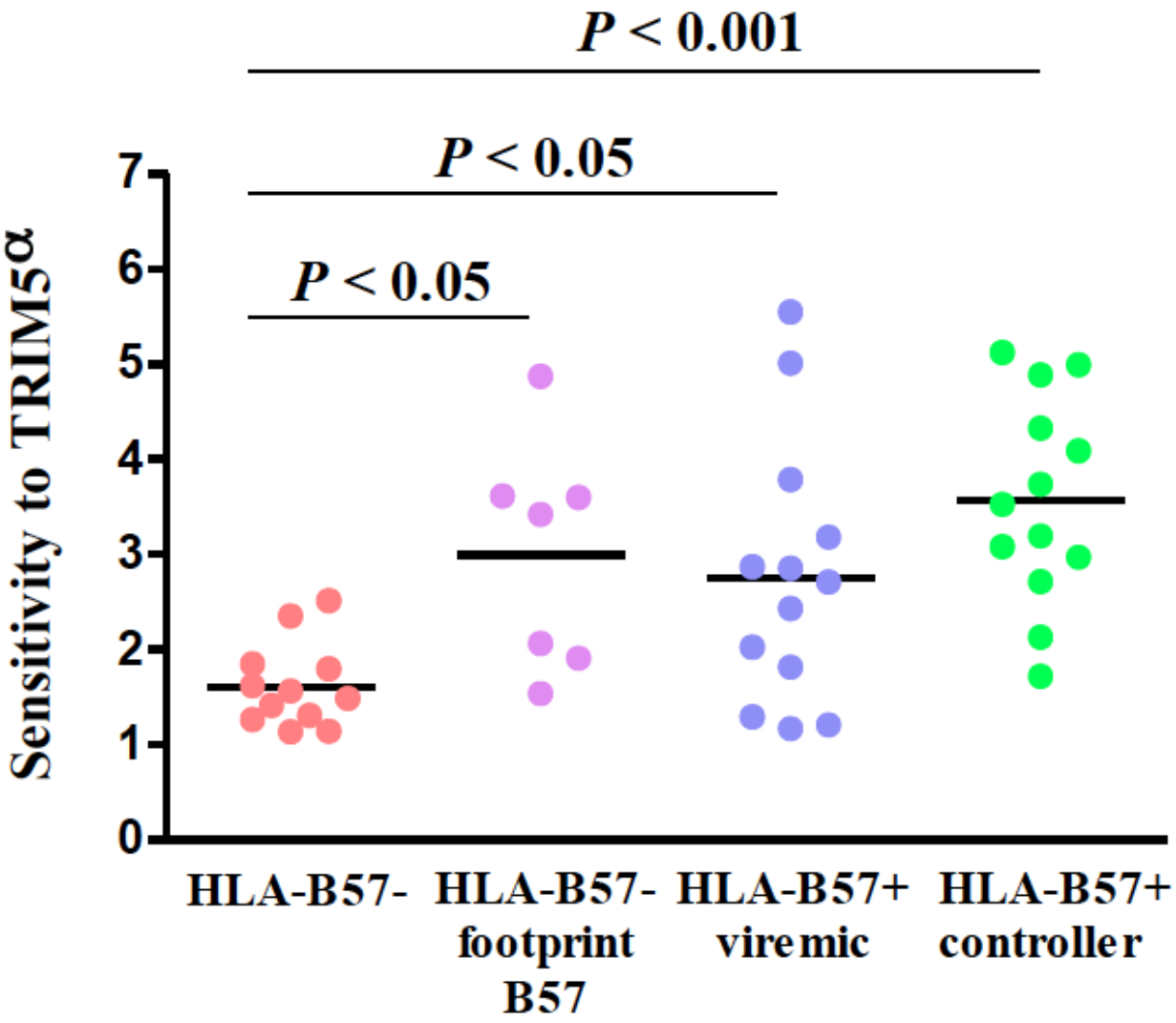


Could conjunct pressure from adaptive and intrinsic immunity participate in HIV-1 replication control *in vivo*?

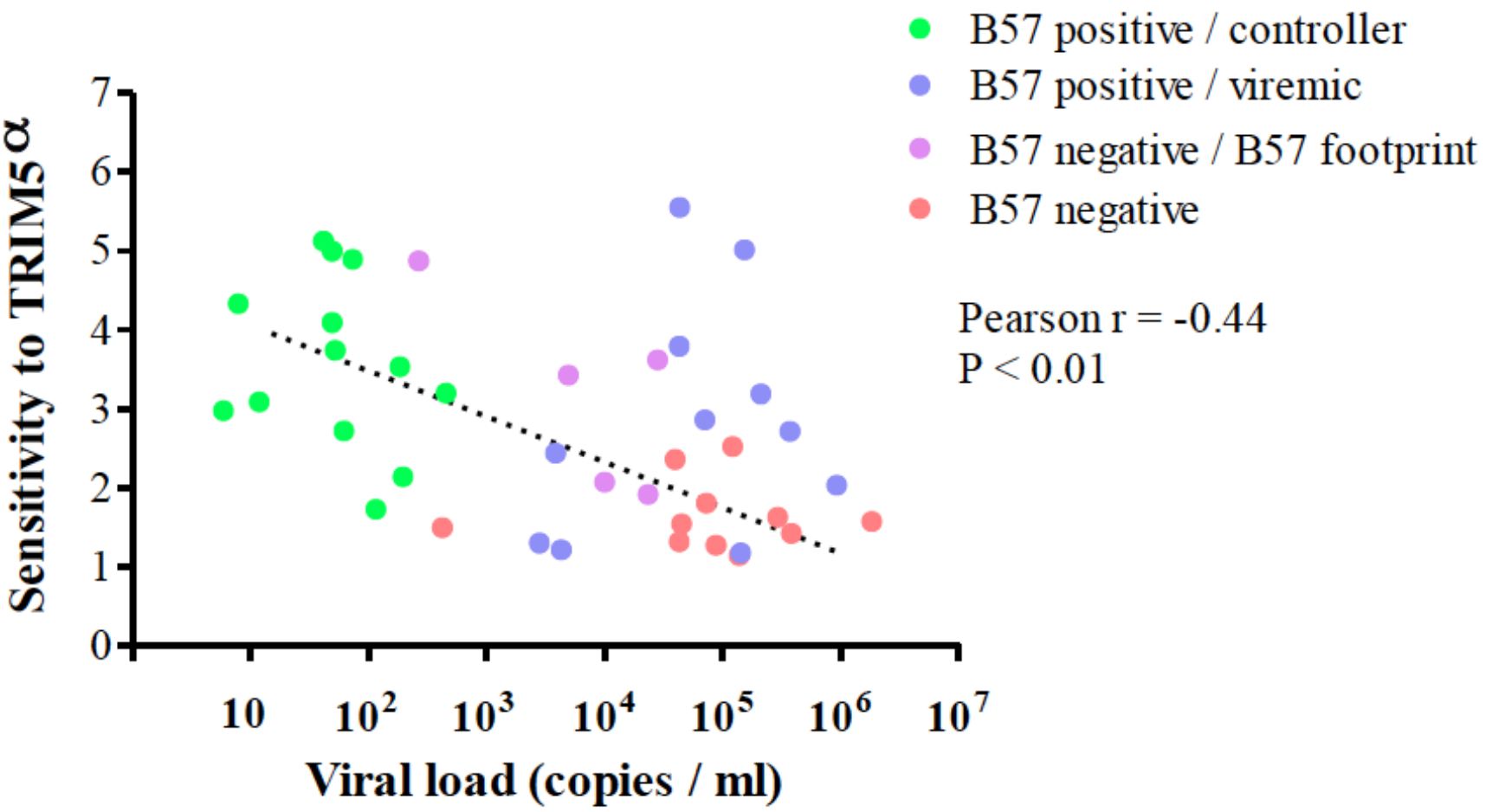
Effect of host HLA genotype



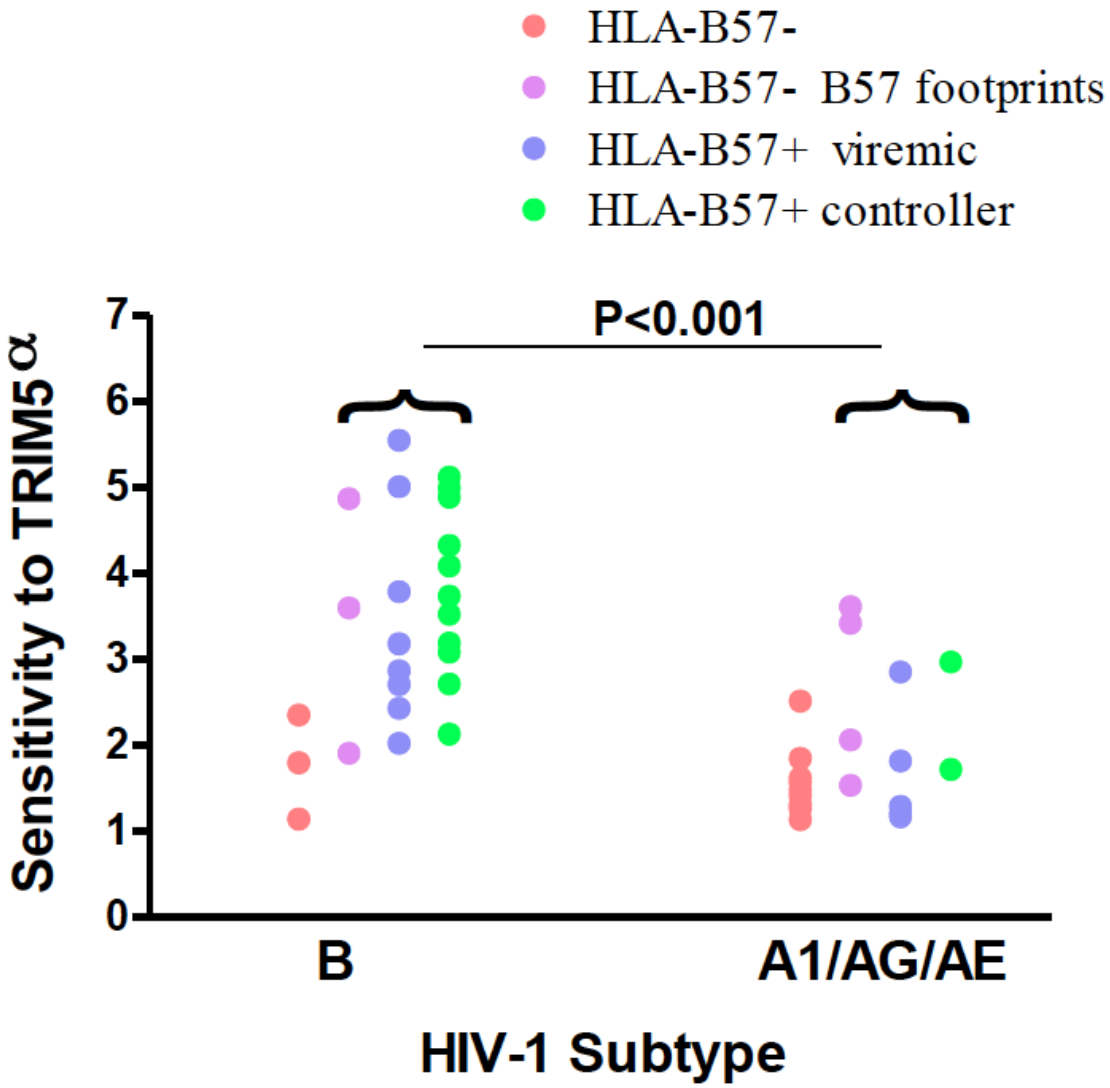
Effect of other parameters



Correlation with viral load

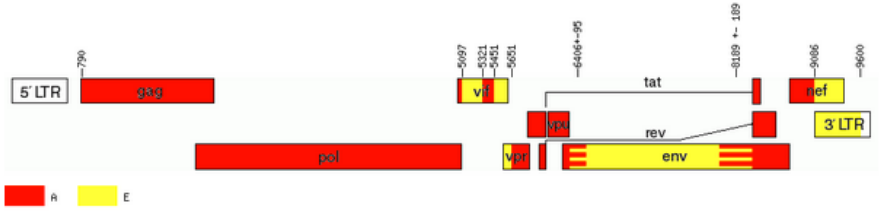


Effect of HIV-1 subtype

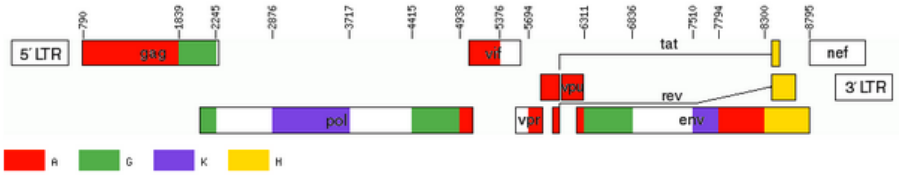


HIV-1 Gag recombinants

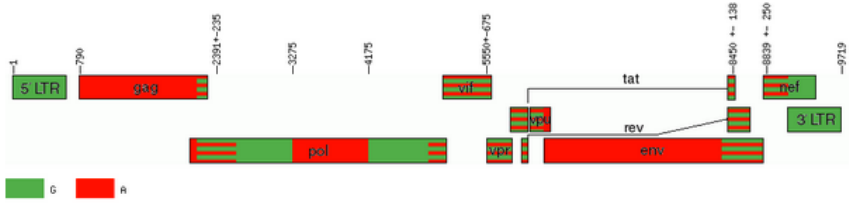
CRF01_AE Reference strain: CM240 Subtypes: A, E



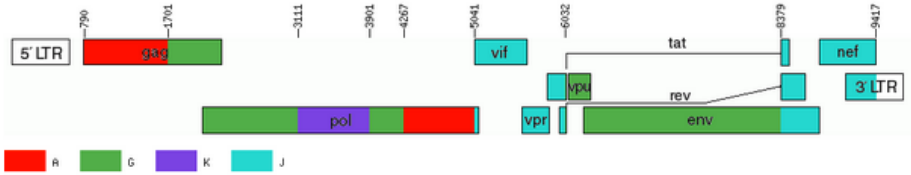
CRF04_cpx Reference strain: 94CY032 Subtypes: A, G, H, K, U



CRF02_AG Reference strain: IbNG Subtypes: A, G

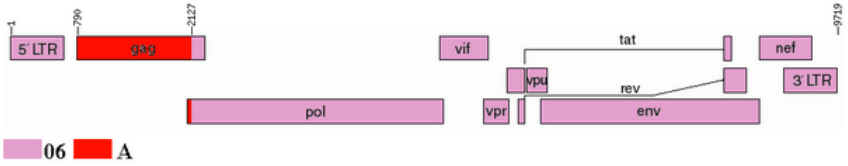


CRF06_cpx Reference strain: BFP90 Subtypes: A, G, J, K

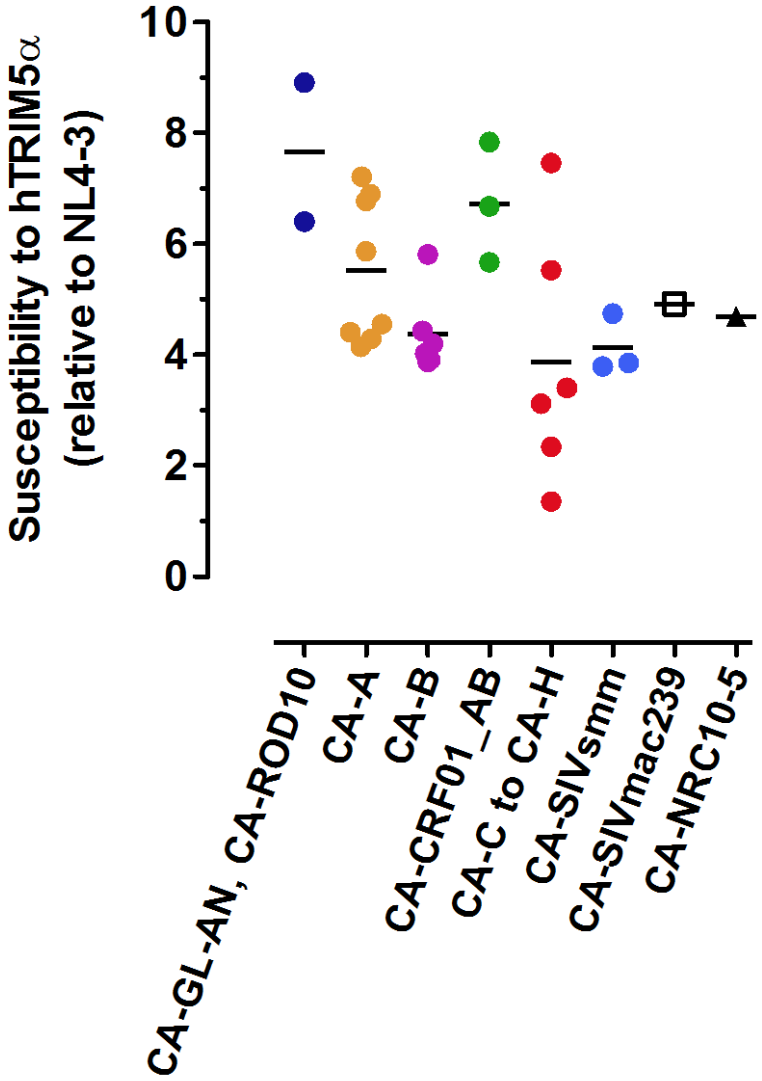


CRF03_AB Reference strain: Kal153 Subtypes: A, B

CRF32_06A1 Reference strain: EE0369 Subtypes: CRF06_cpx, A1



HIV-2



Shibata et al. Retrovirology 2013

Conclusions

- Primary HIV-1 Gag sequences can be markedly sensitive to human TRIM5α
- Gag mutations conferring resistance to some HLA-B restricted CTL response can strongly increase HIV-1 susceptibility to TRIM5α
- Susceptibility to TRIM5α participates in HIV-1 control *in vivo*
- Some viruses do not evolve efficient CTL escape mutations because of potential pressure by TRIM5α
- Susceptibility to TRIM5α is highly context-dependent (HIV-1 subtypes, HLA imprinting, HIV-2, etc.)

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