#228 Differential Down-Regulation of HLA Class I Allotypes by HIV-1 Nef Primary Isolates

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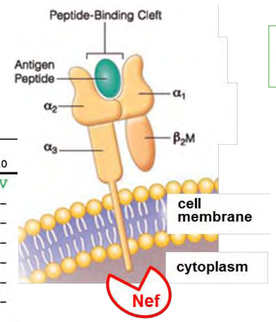
Background

HIV-1 Nef, in conjunction with the host adaptor protein 1 (AP1), binds to the cytoplasmic region of HLA-A and HLA-B molecules and down-regulates them from the cell surface, thus allowing virus-infected cells to evade immune detection. Polymorphic residues within the HLA class I cytoplasmic region may affect Nef binding and subsequent down-regulation. However, the impact of HLA polymorphisms on recognition by primary Nef isolates, and the specific Nef regions responsible for flexible or differential down-regulation of various HLA-A and HLA-B molecules remain incompletely known.

Looking at the cytoplasmic tails of HLA-I

HIV-1 Nef binds to the cytoplasmic tail of HLA class I for down-regulation, leading to immune evasion from CTLs.

Question:
Does the polymorphic nature of this region of HLA-I affect Nef-mediated down-regulation?



Classical HLA I	Allele Name	Amino acid sequence 310	340
HLA-A	A*02	RRKSSDRKGGSYSQAASSDSAQGSDVSLTACKV	
	A*11	----------T----------	
	A*33	----------M----------	
	A*24	--N----------	
	A*43	----------F----------M----------	
	A*80	-K---V----------	
	A*32	----L----------M----------	
HLA-B	B*35	-----GG----------	
	B*57	-----GG---------C----------	

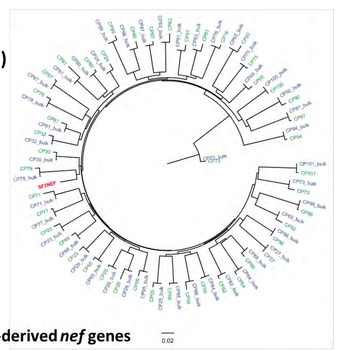
Study design

Chronic progressor cohort

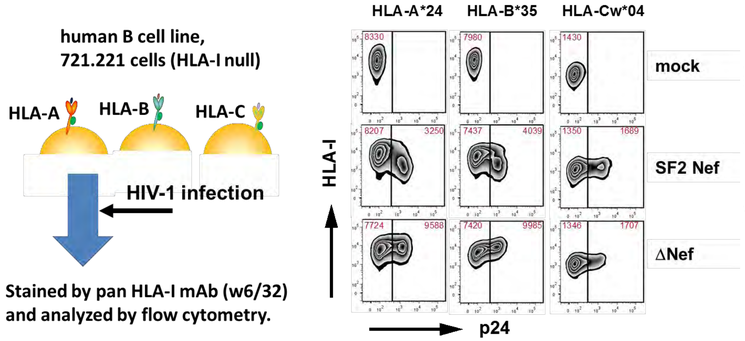
North America, 46 samples (untreated)
CD4 count: median 292 (2-659)
viral load: median 4.90 (2.3-5.9)

Cloning *nef* genes and ligated into proviral clone, pNL43.

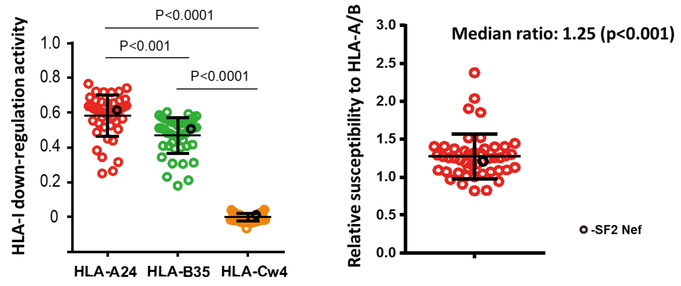
Prepare recombinant viruses carrying patient-derived *nef* genes



① Differential down-regulation of HLA-A/B by laboratory-adapted Nef strain



② Differential down-regulation of HLA-A/B by patient-derived Nef clones



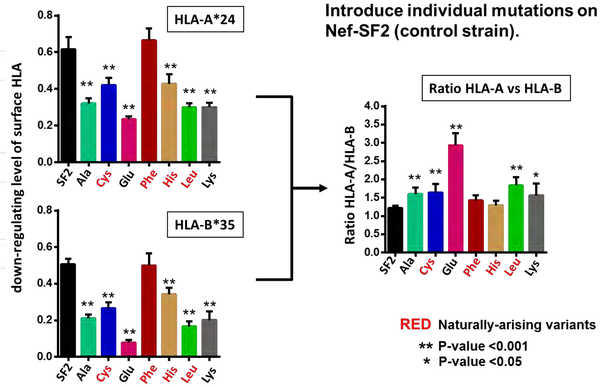
- HLA–B*35 was more resist for down-regulation than HLA-A*24.
- No *nef* gene appeared to affect HLA-Cw*04 expression level.

③ Nef residues associated with differential down-regulation of HLA-A and HLA-B

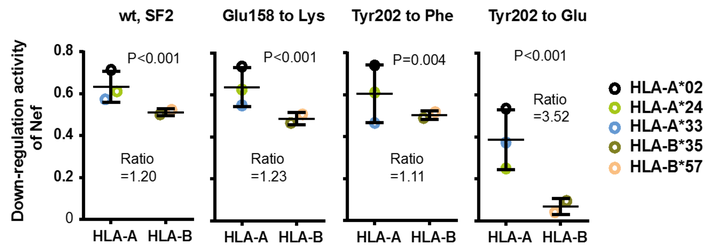
Codon HXB2	AA	HLA-A/HLA-B ratio		no. subjects		p-value	q-value
		AA+	AA-	AA+	AA-		
158	Glu	1.3	1.07	33	12	<0.01	<0.2
202	Tyr	1.23	1.65	40	6	<0.01	<0.2

These two amino acid residues show significant association with differential activity to Nef-mediated HLA-A and HLA-B down-regulation.

④ Functional effects of various Nef-202 mutations

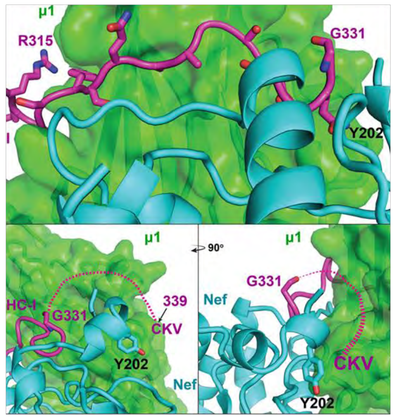


⑤ Differential effects of Nef-202 on various HLA

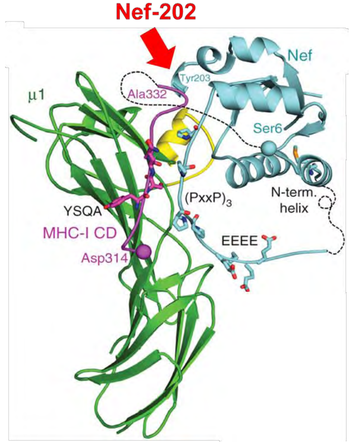


Nef amino acid at 202 is responsible for differential recognition of HLA-I cytoplasmic tails.

⑥ Structural implication between Nef-HLA interaction



Nef-202



Conclusions

- **HLA-B was more resistance, compared to HLA-A, to down-regulation by patient-derived primary Nef clones.**
- **No primary Nef clone down-regulated HLA-C.**
- **Nef polymorphisms at 202 were associated with differential HLA-A and HLA-B down-regulation.**
- **Such preferential down-regulation of HLA-A by patient-derived Nef clones may influence immuno-dominance of HLA-restricted antiviral CTL responses in vivo.**

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