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Structural Dynamics of HIV-1 Envelope Gp120 Outer Domain with V3 Loop

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Abstract

Background: The net charge of the hypervariable V3 loop on the HIV-1 envelope gp120 outer domain plays a key role in modulating viral phenotype. However, the molecular mechanisms underlying the modulation remain poorly understood.

Methodology/Principal Findings: By combining computational and experimental approaches, we examined how V3 net charge could influence the phenotype of the gp120 interaction surface. Molecular dynamics simulations of the identical gp120 outer domain, carrying a V3 loop with net charge of +3 or +7, showed that the V3 change alone could induce global changes in fluctuation and conformation of the loops involved in binding to CD4, coreceptor and antibodies. A neutralization study using the V3 recombinant HIV-1 infectious clones showed that the virus carrying the gp120 with +3 V3, but not with +7 V3, was resistant to neutralization by anti-CD4 binding site monoclonal antibodies. An information entropy study shows that otherwise variable surface of the gp120 outer domain, such as V3 and a region around the CD4 binding loop, are less heterogeneous in the gp120 subpopulation with +3 V3.

Conclusions/Significance: These results suggest that the HIV-1 gp120 V3 loop acts as an electrostatic modulator that influences the global structure and diversity of the interaction surface of the gp120 outer domain. Our findings will provide a novel structural basis to understand how HIV-1 adjusts relative replication fitness by V3 mutations.

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Introduction

The third variable (V3) element of the human immunodeficiency virus type 1 (HIV-1) envelope gp120 protein is usually composed of 35 amino acids. The element forms a protruding loop-like structure on the gp120 outer domain [1], is rich in basic amino acids, and has aromatic amino acids for the aromatic stacking interaction with proteins. The V3 loop participates in direct binding to the entry coreceptor [2] and constitutes the most critical determinant for the coreceptor use of HIV-1 [3,4,5,6]. In addition, the tip of V3 is highly immunogenic and contains neutralization epitopes for antibodies [7,8,9], although the epitopes can be inaccesible in the gp120 trimer on a virion of the HIV-1 primary isolates [10,11] or HIV-1 recombinants with less positively charged V3 [12,13]. Moreover, the V3 is reported to be the major determinant of HIV-1 sensitivity to neutralization by the soluble form of CD4 [14,15,16], a recombinant protein that binds to the cleft of the gp120 core [17]. Thus, the V3 loop plays a key role in modulating biological and immunological phenotypes of HIV-1. However, the molecular mechanisms underlying these modulations remain poorly understood.

It has been reported that the net charge of the V3 loop is tightly linked to the phenotype of HIV-1. The V3 loops of CCR5 tropic HIV-1s are usually less positively charged than those of CXCR4 tropic HIV-1s [18,19,20,21]. An increase in the V3 net charge can convert CCR5 tropic viruses into CXCR4 tropic viruses [4,22,23,24], and antibody resistant viruses into sensitive viruses [12,13]. Thus the V3 loop may be viewed as an electrostatic modulator of the structure of the gp120 interaction surface, an assumption that is largely unexamined.

Increasing evidence has indicated that the dynamics property of molecules in solution is critical for protein function and thus for many biological processes [25,26,27]. Molecular dynamic (MD) simulation is a powerful method that predicts the structural dynamics of biological molecules in solution, which is often difficult to analyze by experiments alone [28,29,30]. Recent advances in biomolecular simulation have rapidly improved the precision and application performance of this technique [28,29,30]. We have previously applied this technique to investigating the structural factors that regulate biological phenotype of viruses [13,31,32]. In this study, by combining MD simulations with antibody neutralization experiments and diversity analysis of the viral protein sequences, we studied a structural basis for the regulation of HIV-1 phenotype by V3 loop.

Results

Molecular dynamics simulation study

To address the potential role of the V3 net charge in modulating the structure and dynamics of the gp120 surface, we performed MD simulations of the identical gp120 outer domains carrying different V3 loops with net charges of +7 or +3 (Fig. 1A). The initial structures for the simulations were constructed by homology modeling using the crystal structure of HIV-1 gp120 containing an entire V3 loop as the template. Due to the perfect identity of the outer domain sequences of the V3 recombinant gp120s, the outer domain structures of the initial models for the MD simulations were identical before the simulations. The modeling targets in this study belong to HIV-1 subtype B and had a sequence similarity of about 87.3% to the modeling template. This similarity was high enough to construct high-accuracy models with an RMSD of ~1.5 Å for the main chain between the predicted and actual structures in the tested cases with homology models and x-ray crystal structures [33]. These initial models were lacking in V1/V2 loops and glycans on the gp120. The recombinant models are therefore suitable for exploring the potency of the structural regulation that is intrinsic to the V3 loop.

Using these models as the initial structures, we analyzed the structural dynamics of the gp120 outer domains in the absence of soluble CD4 by MD simulation. It was expected that the MD simulations would eliminate initial distortions in the template crystal structure, which could be generated during crystallization, and search for the most stable structures of unliganded gp120 outer domains at 1 atm at 310 K in water. The simulations showed that the same gp120 outer domains, carrying different V3 loops with net charges of +7 or +3, exhibited marked changes in conformations and fluctuations at several functional loops at 1 atm at 310 K in water (Figs. 1 and 2).

To quantitatively monitor the overall structural dynamics of the outer domain during MD simulation, the RMSDs between the initial model and models at given times of MD simulation were measured. The RMSD sharply increased soon after heating of the initial model and then gradually reached a near plateau after 10 ns of the MD simulations (Fig. 1B). The results suggested that most of the backbone heavy atoms of the outer domain reached a thermodynamic equilibrium after 10 ns of the simulation under the conditions employed. However, fluctuations of the RMSDs were still detectable even at around 30 ns of the simulations, suggesting that some regions of the outer domains continued to fluctuate.

To map the heavily fluctuating sites in the gp120 outer domain, we calculated the RMSF of the main chains of individual amino acids during the MD simulations. The RMSFs, which provide information about the atomic fluctuations during MD simulations [34], were found to be much greater in the amino acids constituting loops than those of the structured regions, such as helixes and β-sheets (Figs. 1C and 1D). These results are consistent with the general observations of proteins in solution, and indicate that the loops of the gp120 outer domain intrinsically possess structural flexibility in water. Notably, the RMSFs in some loops were markedly different between the two V3 recombinant gp120s. For example, the RMSF in the β20–β21 loop was much greater in the $Gp120_{LAI\text{-}TH09V3}$ (Fig. 1C). Conversely, those in the D loop were greater in the $Gp120_{LAI\text{-}NH1V3}$.

HIV-1 gp120 V3 loop often has a motif for the N-linked glycosylation that is usually preferentially conserved in R5 viruses (Fig. 1A). To address potential impacts of the glycan on the MD simulations, we performed MD simulation in the presence of a high mannose oligosaccharide in the V3 loop. We observed any significant differences in the structure and dynamics of gp120 outer domain in the presence or absence of the glycan (data not shown). This is reasonable because the glycosylation site is exposed toward an opposite direction from the gp120 core (Fig. 1D).

To clarify structural differences between the $Gp120_{LAI\text{-}NH1V3}$ and $Gp120_{LAI\text{-}TH09V3}$, we constructed their averaged structures using the 40,000 snapshots obtained from 10–30 ns of MD simulations using ptraj module in Amber 9. Superposition of the averaged structures showed that the relative configuration of the V3 loops and β20–β21 was markedly different between the two outer domains: the V3 tip protruded a greater distance from the β20–β21 loop in the $Gp120_{LAI\text{-}TH09V3}$ than in the $Gp120_{LAI\text{-}NH1V3}$ (Fig. 2A). The superposed structures also revealed differences in a region around the CD4 binding site (Fig. 2A, right panel with enlarged CD4 binding site). The relative configuration of the CD4 binding loop to the exit loop is critical for the gp120 binding to the CD4, a primary infection receptor of HIV-1 [17]. Therefore, we analyzed the distance between the CD4 binding and exit loops by measuring the distance ($D_{115\text{-}221}$) between the Cα of Gly115 and the Cα of Gly221 as an indicator (Fig. 2B). As expected from the fluctuations of the CD4 binding loop, the $D_{115\text{–}221}$ fluctuated during the MD simulations (Fig. 2C). However, the $D_{115\text{-}221}$ was significantly smaller in the $Gp120_{LAI\text{-}TH09V3}$ than in the $Gp120_{LAI\text{-}NH1V3}$ (Fig. 2D; $p<0.001$, Student's *t*-test): the $D_{115\text{–}221}$ ranged from 4–15 Å with an average of ~8 Å for the $Gp120_{LAI\text{-}TH09V3}$ and from 7–17 Å with an average of ~10 Å for the $Gp120_{LAI\text{-}NH1V3}$. These data suggest that the CD4 binding loop tended to be positioned more closely to the exit loop and thus tended to be sterically less exposed in the $Gp120_{LAI\text{-}TH09V3}$ than the $Gp120_{LAI\text{-}NH1V3}$.

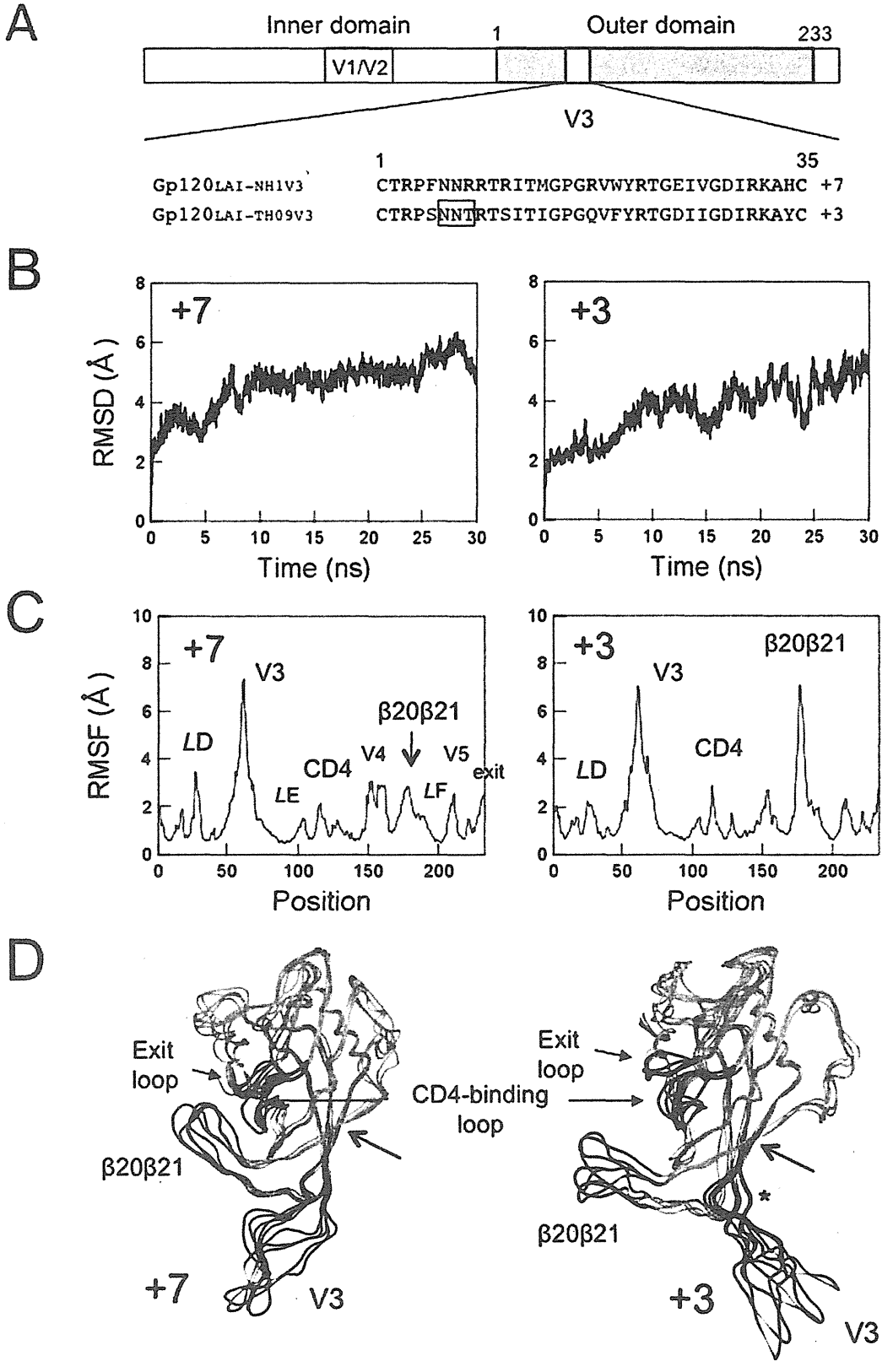
Neutralization study

The above structural data raised the possibility that the reduction in the V3 net charge might reduce HIV-1 neutralization sensitivity by the anti-CD4 binding site antibodies. To address this possibility, we performed a neutralization assay using the two isogenic HIV-1 recombinant viruses, $HIV\text{-}1_{LAI\text{-}NH1V3}$ and $HIV\text{-}1_{LAI\text{-}TH09V3}$ [35], which carry the $Gp120_{LAI\text{-}NH1V3}$ and $Gp120_{LAI\text{-}TH09V3}$, respectively. These viruses were pre-incubated with various human MAbs against the CD4 binding site, and the reductions in viral infectious titers were measured using a HeLa-cell-based single-round viral infectivity assay system [36].

Table 1 summarizes the results of the neutralization assay. As expected, the two viruses exhibited markedly distinct neutralization sensitivities to the three human MAbs against the CD4 binding site. $HIV\text{-}1_{LAI\text{-}NH1V3}$ was consistently neutralized with all three MAbs against the CD4 binding site (49G2, 42F6, and 0.5δ), with ND_{50} values ranging between 0.224 and 0.934 μg/ml. In marked contrast, $HIV\text{-}1_{LAI\text{-}TH09V3}$ was highly resistant to neutralization by these MAbs, and 10 μg/ml of antibodies failed to block the viral infections. The two viruses were equally resistant to an anti-Gp120 antibody (4C11) that recognizes the Gp120 structure after CD4 binding. The result indicates that the CD4-induced gp120 epitope of the 4C11 are not preserved in the V3 recombinant viruses used in the present study. Conversely, they were equally sensitive to another ant-Gp120 antibody (4301 [37]) whose epitope is located outside of the CD4 binding site. A human MAb 8D11 used as a negative control had no effect on the viral infectivity in this assay.

Diversity study

Host immunity is a driving force behind the antigenic diversity of envelope proteins of the primate lentiviruses that establish persistent infection in hosts [23,38,39,40,41]. The above and


A
Inner domain
1
Outer domain
233
V1/V2
V3
1
35
Gp120LAI-NH1V3 CTRPFNNRRTRITMGPGRVWYRTGEIVGDIRKAHC +7
Gp120LAI-TH09V3 CTRPSNNTRTSITIGPGQVFYRTGDIIGDIRKAYC +3
B
+7
+3
RMSD (Å)
Time (ns)
C
RMSF (Å)
+7
V3
LD
β20β21
CD4
V4
V5
exit
LE
LF
+3
β20β21
V3
CD4
LD
Position
D
Exit loop
CD4-binding loop
β20β21
+7
V3
+3
V3