

3D Models for Conformational States of the V3 and V1/V2 Loops in gp120/CD4/Antibody Complex

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Introduction

The X-ray structure of the ternary complex of an engineered “core” gp120, CD4 and an antibody [1] does not contain the hypervariable V3 and V1/V2 loops (the gp120₂₉₈₋₃₃₁ and gp120₁₂₆₋₁₉₆ fragments, respectively). These loops are extremely important in HIV function. We have restored several feasible 3D structures of these loops in gp120 applying a computational approach based on residue-residue contact matrices.

Results and Discussion

3D structures of the V3 and V1/V2 loops were restored by the procedure described elsewhere [2] that consists of the following steps: (i) prediction of coordination numbers for each loop residue (*i.e.*, the numbers of contacts between loop residues within the loop and with the “core” residues), a contact being defined as the $C_i^\alpha - C_j^\alpha$ distance $< 8 \text{ \AA}$; (ii) calculation of *a priori* probabilities of residue-residue contacts as functions of coordination numbers; (iii) calculation of the residue-residue contact matrices under conditions that ensure generation of matrices corresponding to sterically consistent 3D structures with appropriate protein density only; (iv) prediction of the matrices of inter-residue distances from the contact matrices; (v) restoring possible 3D structures of C^α -traces for the loops by a distance geometry algorithm starting from predicted inter-residue distances; (vi) generating additional possible C^α -traces by finding subfragments that are mirror images of a given 3D structure still in compliance with the contact matrix.

The above procedure resulted in the reconstruction of 8 different C^α -traces for the loop V1/V2 and 6 different conformers for the loop V3. Figure 1 depicts the 3D structure of gp120 with both restored loops (the calculated loop structures of type 1 are shown). In all 8 structures predicted for the V1/V2 loop, there are contacts of loop res-

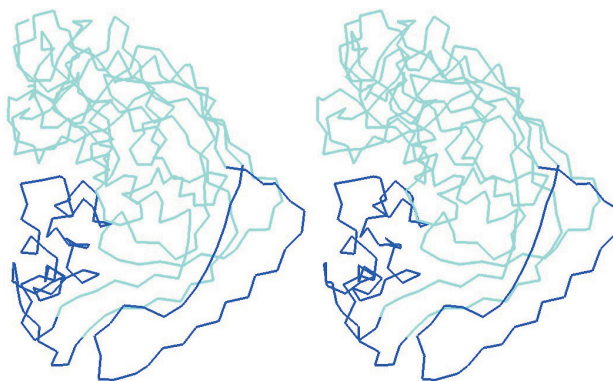


Fig. 1. Stereoview of 3D structure of gp120 with restored V3 (right) and V1/V2 (left) loops. In both cases, the calculated structures of type 1 are presented. Loops are shown in black.

Analytical Methods

idues with 10 to 25 out of 26 residues of the “core” gp120 that are in direct contact with CD4 according to the X-ray structure of the gp120/CD4/antibody complex [1]. For instance, the V1/V2 loop structure of type 1 contacts 25 out of the 26 mentioned residues of the “core” gp120, namely L125, D279, N280, A281, T283, S365, G366, G367, D368, E370, I371, N425, M426, W427, Q428, K429, V430, T455, R456, D457, G458, R469, G472, G473 and D474. Residues in the various structures of the V3 loop contact from 11-13 out of the 15 residues of the “core” gp120 that have been suggested to contact the co-receptor (CCR5) according to site-directed mutagenesis [3].

The V3 loop structure of type 1 contacts K121, T123, H330, R419, I420, K421, Q422, P437, P438, S440, G441, Q442 and R444.

The restored structures of the V1/V2 loop very effectively shield the gp120 cavity that is occupied by CD4 in the X-ray structure of the gp120/CD4/antibody complex, whereas the restored structures of the V3 loop cover the gp120 surface that presumably binds the HIV co-receptor. These observations validate the results of our calculations, since they are in agreement with the widely accepted hypothesis describing the HIV binding to the cell membrane (*e.g.*, [4]). First, CD4 binds gp120 on the viral envelope displacing the V1/V2 loop from the surface of gp120. This binding induces conformational changes in gp120 including movement of the V3 loop, which exposes the co-receptor-binding sites of gp120. It is noteworthy also that the computational approach based on the residue-residue contact matrices was able to restore large loops on the protein surface (up to 69 residues, as in the V1/V2 loop).

Acknowledgments

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References

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