Computational design of entry inhibitor scaffolds targeting the third variable loop of HIV-1 gp120

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The HIV-1 cell entry is mediated by the sequential interactions of the envelope protein gp120 with the receptor CD4 and a co-receptor, usually CCR5 or CXCR4, depending on the individual virion, and the third variable (V3) loop of gp120 is critically involved in this process (reviewed in [1]). In this context, the strategy to develop anti-HIV-1 drugs based on co-receptor antagonists to efficiently mask this functionally important site of gp120 is highly challenging [1].

In this study, novel anti-HIV-1 agents targeting the V3 loop of envelope protein gp120 were designed by computer modeling based on glycosphingolipid β-galactosylceramide (β-GalCer), which is an alternative receptor allowing HIV-1 entry into CD4-negative cells of neural and colonic origin [2]. In doing so, the following problems were solved: (i) twelve novel β-GalCer derivatives containing different substitutes of the glycolipid fatty acid residue were generated by computer graphics tools and their 3D structures were determined by quantum chemistry calculations; (ii) structural complexes of these glycolipids with the HIV-1 V3 loops from five different viral variants were built by molecular docking and analysis of intermolecular interactions responsible for their energy stabilization was carried out; (iii) stability of the complexes of interest was estimated by molecular dynamics simulations and binding free energy calculations.

The starting models of the β-GalCer analogs were designed by substitution of β-GalCer fatty acid residue by different soluble acids. Quantum chemical calculations of the 3D structures for the β-GalCer analogs were performed by the GAUSSIAN 09 program package. The 3D structures of the V3 loops from five different HIV-1 modifica-

tions [3] were used as static receptors for flexible ligand docking of the β-GalCer analogs by the AutoDock VINA program. The docked structures of these glycolipids with V3 were exposed to energy refinement followed by molecular dynamics simulations within 30 ns, which were carried out by the Amber 11 computer package using the Amber ff10 force field. The free energy of binding was used as a measure of conformational stability of the complexes of interest and was calculated by the MM-PB/SA procedure in AMBER 11.

As a result, the designed compounds were found to block the tip and/or the base of the V3 loop, which form invariant structural motifs that contain residues critical for cell tropism [1]. Specific binding to the V3 loop was accomplished primarily by non-conventional XH···π interactions between CH/OH sugar groups of the glycolipids and the conserved V3 residues with π-conjugated side chains. Along with XH···π interactions, π-stacking and the standard H-bonds involving the functionally important residues of the V3 loop greatly contribute to forming the complexes of the designed β-GalCer analogs with this site of gp120. With the molecular dynamics simulations, the docked models of the complexes of the β-GalCer analogs with V3 are energetically stable in all of the cases of interest and exhibit low values of free energy of their formation.

Based on the data obtained, the designed glycolipids are supposed to provide promising entry inhibitor scaffolds for the design of novel, potent and broad antiretroviral drugs to neutralize HIV-1.

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