Pharmacophore-based virtual screening of novel HIV-1 fusion inhibitors mimicking potent and broad neutralizing antibody 10e8

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Discovery of anti-HIV-1 broadly neutralizing antibodies (bNAbs) blocking the virus entry provided a new strategy in vaccine and drug design [1]. In particular, studies on the identification of small molecules able to mimic pharmacophore properties of anti-HIV-1 bNAbs are of great interest.

In this work, pharmacophore-based virtual screening of entry inhibitor scaffolds mimicking anti-HIV-1 bNAb 10e8 [2] was carried out followed by evaluation of their potential neutralizing activity using molecular modeling. 10e8 is one of the most potent and broad HIV-neutralizing antibodies isolated and it neutralizes up to 98% of diverse HIV-1 strains by specific interactions with the membrane-proximal external region (MPER) of the envelope protein gp41. This tryptophan-rich region of gp41 is critical for Env-mediated fusion and virus infectivity [2]. In combination with other antibodies 10e8 may provide an antibody response that neutralizes nearly all strains of HIV-1 [2].

To reach the goal of this study, the amino-acid residues of bNAb 10e8 responsible for specific binding to gp41 were determined by molecular dynamics simulations of the X-ray structure of this antibody Fab in the complex with the HIV-1 MPER peptide [2]. Based on these residues, pharmacophore models describing different combinations of the antibody binding hot spots were built and used as the input dataset for identification of peptidomimetic candidates of bNAb 10e8 by a public web-oriented virtual screening platform (pepMMsMIMIC) associated with the MMsINC database [3]. Complexes of these candidates with gp41 were generated by molecular docking and their stability was estimated by molecular dynamics simulations and binding free energy calculations.

The molecular dynamics simulations of the twenty top-ranking docked complexes between the 10e8 potential peptidomimetics and gp41 revealed eight molecules that exposed negative binding free energy values. These molecules were therefore selected for the final analyses. With these analyses, the high affinity of their binding to gp41 occurs by intermolecular π-π interactions and van der Waals contacts involving conserved tryptophan residues of the MPER segment. These residues of gp41 play important role in the fusion of viral and target cell membranes [2]. At the same time, specific binding to gp41 is accomplished primarily by π-π interactions between the aromatic rings of peptidomimetic candidates and Trp-672 of the MPER segment, a key residue of linear epitope of 10e8 [2]. In a mechanism similar to that of bNAb 10e8, these compounds block the central hinge region of the MPER peptide providing the conformational flexibility necessary for the Env-mediated hemifusion and fusion processes [2]. The docked structures of the identified molecules with gp41 do not undergo substantial rearrangements during the molecular dynamics simulations, in agreement with the low values of free energy of their formation. Finally, these small molecules match Lipinski's Rule-of-Five describing molecular properties important for a drug's pharmacokinetics in the human body [4].

In light of the findings obtained, the identified compounds are considered as promising scaffolds for the design of novel, potent and broad anti-HIV-1 drugs that inhibit the membrane fusion by targeting the MPER segment of the HIV-1 coat protein gp41.

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References

1. Van Gils, M.J., Sanders, R.W.: Broadly Neutralizing Antibodies Against HIV-1: Templates for a Vaccine. Virology. 435, 46–56 (2013).
2. Huang, J., Ofek, G., Laub, L. et al.: Broad and Potent Neutralization of HIV-1 by a gp41-Specific Human Antibody. Nature. 491, 406–412 (2012).
3. Floris, M., Masciocchi, J., Fanton, M., Moro, S.: Swimming into Peptidomimetic Chemical Space Using pepMMsMIMIC. Nucl. Acids Res. 39 (suppl. 2), W261–W269 (2011).
4. Lipinski, C.A., Lombardo, F., Dominy, B.W., Feeney, P.J. Lead- and Drug-Like Compounds: the Rule-of-Five Revolution. Adv. Drug Delivery Rev. 46, 3–26 (2001).