***In silico* Analysis of Interactions between Nevirapine-related Compounds, *HLA-B*14:02* and T-cell Receptor**

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(Received April 26; accepted May 27; published online July 1, 2016)

Abstract

A non-nucleoside reverse-transcriptase inhibitor nevirapine (NVP) used to treat HIV-1 infection can cause severe, life-threatening idiosyncratic drug toxicity (IDT). It is known that the IDT caused by NVP or its metabolites is associated with the *HLA-B*14:02* haplotype. The molecular mechanism of the *HLA*-associated IDT, however, has not been disclosed. In this study, we have simulated the interaction modes between NVP-related compounds, *HLA-B*14:02*, and a T-cell receptor in order to understand the molecular mechanism leading to the onset of IDT.

Key Words: nevirapine, idiosyncratic drug toxicity, *HLA-B*14:02*, T cell receptor, docking simulations

Area of Interest: *In silico* drug discovery

1. Introduction

A non-nucleoside reverse-transcriptase inhibitor nevirapine (NVP) is widely used as a first-line treatment of patients infected with human immune-deficiency virus. Approximately 5% of NVP-treated individuals develop allergic reactions with symptoms of idiosyncratic drug toxicities (IDTs). In rare cases, these side effects can be fatal [1].

The utility of *HLA* typing in HIV patients to identify genetic factors that may confer susceptibility to IDT has demonstrated that the reaction is associated with the *HLA-B*14:02* haplotype [2]. The molecular mechanisms of such IDT associated with a specific *HLA* allele have not been fully disclosed. However, it is considered that binding of a relevant drug or its metabolites to the pertinent *HLA* molecule triggers the IDT [3]. The chemical structures of the major metabolites of NVP reported to date [4][5] and NVP are given in Figure 1. Hereafter, these NVP-related compounds will be collectively referred to as NVP-RCs. Since the binding affinities and the binding modes of these compounds to the *HLA* molecules have not been clarified yet, it is not still clear which compound

should be associated with the onset of IDT. In this study, docking simulations between these compounds and the *HLA-B*14:02* molecule have been performed in order to identify the potential compounds responsible for IDT. Hereafter the complex between a NVP-RC and the *HLA-B*14:02* molecule is briefly referred to as NVP-RC/*B1402*. We also simulated the interaction mode of NVP-RC/*B1402* with a T-cell receptor to understand the activation mechanism of the T-cell receptor by contact with a NVP-RC/*B1402*.

Figure 1. Chemical structures of nevirapine and its metabolites

2. Methods

A crystal structure of *HLA-B*14:02* (PDB ID: 3BXN) deposited at the Protein Data Bank [6] was used in this study. Docking simulations between NVP-RC and *HLA-B*14:02* were performed by use of a docking software ASedock [7]. The binding affinity was judged by a scoring function of GBVI/WSA_dG which is considered to express protein-ligand binding free energy [8].

The crystal structure of the complex between the LC13 T-cell receptor, *HLA-B*08:01* and an antigenic peptide (PDB ID: 1MI5) was used to construct the 3D model of the complex between the LC13 T-cell receptor and NVP-RC/*B1402*. The sequence identity of the alpha chains of *HLA-B*14:02* and *HLA-B*08:01* is 95.7%, and the root mean square deviations of the corresponding main chain atoms is 1.20 Å. It indicates that these structures are sufficiently similar. Therefore, the initial model of the complex between LC13 and NVP-RC/*B1402* (hereafter LC13/ NVP-RC/*B1402*) was constructed by superposing the main chain atoms of the *HLA-B*14:02* and *HLA-B*08:01* molecules. The structure of the ternary complex of NVP-RC/*B1402*/LC13 have been optimized using the force field of MMFF94x[9] until the energy gradient drops below 0.01 kcal/(mol· Å).

A software system MOE (molecular operating environment) [10] was used throughout this study.

3. Results and Discussion

The lowest GBVI/WSA_dG values (kcal/mol) of the complexes between *HLA-B*14:02* and

NVP-RCs are as follows: 8-OH-NVP -6.77, 4-COOH-NVP -6.76, 2,3-epoxide-NVP -6.58, 3,4-epoxide-NVP -6.40, NVP -6.40, 3-OH-NVP -6.08, 2-OH-NVP -6.06, 12-OH-NVP -5.93, QM -5.57. The structure of the complex of 4-COOH-NVP/*B1402* is shown in Figure 2.

Figure 2. Binding mode of 4-COOH-NVP to *HLA-B*14:02*
The structure of *HLA-B*14:02* is depicted in cartoon mode, and 4-COOH-NVP in ball-and-stick model. The T-cell receptor approaches from the top.

Figure 3. The ternary complex of 4-COOH-NVP/*HLA-B*14:02*/LC13

The structures of *HLA-B*14:02* and LC13 are depicted in cartoon mode, and 4-COOH-NVP (green) and Tyr100 (cyan) in ball-and-stick model. A dotted line indicates a hydrogen bond.

the ternary complex of 4-COOH-NVP/*B1402*/LC13 is shown in Figure 3. The lower and upper protein parts represent *HLA-B*14:02* and LC13, respectively. The carboxyl group exposed on the surface of *HLA-B*14:02* is hydrogen-bonded to Tyr100. In the crystal structure of LC13/*HLA-B*08:01*/antigenic peptide (PDB ID: 1MI5) [11], the backbone carbonyl oxygen atom of Gly8 of the antigenic peptide (FLRGRAYGL) is also exposed on the surface of *HLA-B*08:01* and hydrogen-bonded to the relevant Tyr100. This structure of the predicted ternary complex suggests that NVP-induced IDT could be caused by direct interaction between TCR and the presented NVP-RC, possibly 4-COOH-NVP, by *HLA-B*08:01*.

Since the binding modes of 4-COOH-NVP and 8-OH-NVP with the highest binding affinities to *HLA-B*14:02* are similar, these metabolites are considered to be primary compounds responsible for IDT. In the crystal structure of the complex between a nucleoside reverse transcriptase inhibitor abacavir and *HLA-B*57:01*, abacavir is bound deeply at the bottom of the antigen-binding groove (PDB ID: 3VRI, 3VRJ) [3]. However, 4-COOH-NVP is bound near the opening of the groove and a part of the 4-COOH-NVP molecule is exposed as shown in Figure 2. It indicates that the interaction modes of abacavir and NVP-RC with the corresponding HLA molecules should be significantly different. As illustrated by the molecular surface in Figure 2, the carboxyl group is exposed on the surface of the HLA molecule suggesting the possible direct interaction with the T-cell receptor.

The three-dimensional structures of the complexes between 4-COOH-NVP/*B1402* and 8-OH-NVP/*B1402*, and the T-cell receptor of LC13 were constructed and optimized in order to assess the modes of interaction. The GBVI/WSA_dG values of 4-COOH-NVP/*B1402*/LC13 and 8-OH-NVP/*B1402*/LC13 are -7.76 and -7.56 kcal/mol, respectively. The structure of

Acknowledgement

This work was partly supported by Grant-in-Aid for Scientific Research on Innovative Areas (22133012) from MEXT (Ministry of Education, Culture, Sports, Science and Technology) for N.H.

References

- [1] Patel, S. M.; Johnson, S.; Belknap, S. M.; Chan, J.; Sha, B. E.; *et al.* Serious adverse cutaneous and hepatic toxicities associated with nevirapine use by non-HIV-infected individuals. *J. Acquir. Immune Defic Syndr.* **2004**, *35*, 120-125.
- [2] Littera, R.; Carcassi, C.; Masala, A.; Piano, P.; Serra, P.; *et al.* HLA-dependent hypersensitivity to nevirapine in Sardinian HIV patients. *AIDS*, **2006**, *20*, 1621-1626.
- [3] Illing, P. T.; Vivian, J. P.; Dudek, N. L.; Kostenko, L.; Chen, Z.; *et al.* Immune self-reactivity triggered by drug-modified HLA-peptide repertoire. *Nature*, **2012**, *486*, 554-558.
- [4] Riska, P.; Lamson, M.; MacGregor, T.; Sabo, J.; Hattox, S.; *et al.* Disposition and biotransformation of the antiretroviral drug nevirapine in humans. *Drug. Metab. Dispos.* **1999**, *27*, 895-901.
- [5] Srivastava, A.; Lian, L. Y.; Maggs, J. L.; Chaponda, M.; Pirmohamed, M.; *et al.* Quantifying the metabolic activation of nevirapine in patients by integrated applications of NMR and mass spectrometries. *Drug. Metab. Dispos.* **2010**, *38*, 122-132.
- [6] Bernstein, F. C.; Koetzle, T. F.; Williams, G. J.; Meyer, E. F. Jr.; Brice, M. D.; *et al.* The protein data bank: a computer based archival file for macromolecular structures. *J. Mol. Biol.* **1977**, *112*, 535-542.
- [7] Goto, J.; Kataoka, R.; Muta, H.; Hirayama, N. ASEDock-docking based on alpha spheres and excluded volumes. *J. Chem. Inf. Model.* **2008**, *48*, 583-590.
- [8] Corbeil, C. R.; Williams, C. I.; Labute, P. Variability in docking success rates due to dataset preparation. *J. Comput. Aided. Mol. Des.* **2012**, *26*, 775-786.
- [9] Halgren, T. A. MMFF VII. Characterization of MMFF94, MMFF94s, and other widely available force fields for conformational energies and for intermolecular-interaction energies and geometries. *J. Comput. Chem.* **1999**, *20*, 730-748.
- [10] MOE (Molecular Operating Environment), 2014.09; Chemical Computing Group: Montreal, Quebec, Canada, **2014**.
- [11] Kjer-Nielsen, L.; Clements, C. S.; Purcell, A.W.; Brooks, A. G.; Whisstock, J. C.; *et al.* A Structural Basis for the Selection of Dominant $\alpha\beta$ T Cell Receptors in Antiviral Immunity. *Immunity*, **2003**, *18*, 53-64.