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

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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 \textit{HAL-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 \textit{HAL-B}\*14:02 molecule is briefly referred to as NVP-RC/B\*1402. We also simulated the interaction mode of NVP-RC/B\*1402 with a T-cell receptor to understand the activation mechanism of the T-cell receptor by contact with a NVP-RC/B\*1402.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{chemical_structures.png}
\caption{Chemical structures of nevirapine and its metabolites}
\end{figure}

2. Methods

A crystal structure of \textit{HAL-B}\*14:02 (PDB ID: 3BXN) deposited at the Protein Data Bank [6] was used in this study. Docking simulations between NVP-RC and \textit{HAL-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, \textit{HAL-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/B\*1402. The sequence identity of the alpha chains of \textit{HAL-B}\*14:02 and \textit{HAL-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/B\*1402 (hereafter LC13/ NVP-RC/B\*1402) was constructed by superposing the main chain atoms of the \textit{HAL-B}\*14:02 and \textit{HAL-B}\*08:01 molecules. The structure of the ternary complex of NVP-RC/B\*1402/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 \textit{HAL-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.

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 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.
Supplements

The atomic coordinates of the following structures in PDB format are available as supplemental data at http://cbi-society.info/supplement/10.1273/cbij-16-3/8-OH-NVP/B1402, 4-COOH-NVP/B1402, 8-OH-NVP/B1402/LC13 and 4-COOH-NVP/B1402/LC13.

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