In silico Analysis of Interactions between HLA-B*58:01 and Allopurinol-related Compounds

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Abstract

Allopurinol, the most traditional and widely used medication for hyperuricemia and gout, has been reported as a common cause of severe cutaneous adverse reactions. Allopurinol is rapidly and extensively metabolized to oxipurinol. At least six allopurinol-related impurities have been reported to be contained in allopurinol. It is of interest to identify the compound which is likely to be responsible to the adverse reactions. Since a strong association between allopurinol-induced adverse reactions and HLA-B*58:01 has been observed, binding of allopurinol-related compounds to HLA-B*58:01 must be important for the onset of the adverse reactions. In this study, using the three-dimensional structure of HLA-B*58:01 constructed by homology modeling, the binding modes and affinities between allopurinol-related compounds and HLA-B*58:01 were simulated by docking simulations. The results have indicated that the adverse reactions of allopurinol should be due very largely to oxipurinol. The results also suggested that the concentrations of several impurities currently approved by the United States Pharmacopeia should be strictly monitored not to exceed the limits because they may strongly bind to HLA-B*58:01 and possibly leading to more severe adverse reactions.

Key Words: allopurinol, idiosyncratic drug toxicity, HLA-B*58:01, docking simulations

Area of Interest: In silico drug discovery

1. Introduction

Allopurinol is effective for the treatment of hyperuricemia and gout. Although allopurinol is one of the most widely used drugs in the world, it is also known as one of the most common causes of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal
necrolysis [1]. There is a strong association between the HLA-B*58:01 and the allopurinol induced adverse reactions [2]. The molecular mechanisms of such idiosyncratic drug toxicity (IDT) associated with a specific HLA allele have not been fully disclosed. However, it is considered that binding of a relevant drug, its metabolites or contained impurities to the pertinent HLA triggers the IDT [3], suggesting that the binding affinity is an important measure of the potential IDT. Allopurinol is rapidly and extensively metabolized to oxipurinol and the hypouricemic efficacy of allopurinol is considered to be due to this metabolite [4]. According to the United States Pharmacopeia, the minimum guaranteed purity of allopurinol is 98.0 and at least six impurities have been identified [5]. It has been unknown which compound is responsible to the IDT. In this study, the binding mode and affinity of allopurinol, oxipurinol and six impurities to HLA-B*58:01 was calculated by docking simulations in order to identify which compound is primarily involved in the IDT reaction. The chemical structures of six impurities together with allopurinol and oxipurinol are shown in Figure 1.

![Chemical structures of allopurinol, its metabolite and the impurities](image)

Figure 1. Chemical structures of allopurinol, its metabolite and the impurities

2. Methods

As the crystal structure of HLA-B*58:01 is not available, the 3D structure was constructed by homology modeling using the software HLA-Modeler [6]. The X-ray crystal structure of the HLA-B*57:01 molecule (PDB ID: 2RFX) deposited at the Protein Data Bank [7] was used as the template structure of HLA-B*58:01. The binding modes and affinities of the allopurinol and its related compounds at the antigenic-peptide binding cleft of HLA-B*58:01 were obtained by
docking simulations by use of ASEDock [8]. Up to ten possible tautomers of all compounds were generated and considered in the docking simulations. As the impurity F can adopt (E) and (Z) configurations, both structures were treated as independent molecules. Hereafter, these nine compounds will be referred to as allopurinol-related compounds (Figure 1).

The binding affinity was judged by a scoring function of GBVI/WSA_dG which is considered to express protein-ligand binding free energy [9]. A software system MOE (molecular operating environment) [10] was used throughout this study. The atomic coordinates in PDB format of all the complexes between HLA-B*58:01 and allopurinol-related compounds with the lowest GBVI/WSA_dG values are deposited as supplemental data.

3. Results and Discussion

The lowest GBVI/WSA_dG values (kcal/mol) of the complexes between HLA-B*58:01 and the allopurinol-related compounds are as follows: allopurinol -5.64, oxipurinol -6.04, impurity A -5.28, impurity B -6.22, impurity C -6.53, impurity D -6.37, impurity E -7.22, impurity (E)-F -9.47, impurity (Z)-F -8.39.

Since allopurinol is rapidly and extensively metabolized to oxipurinol after administration and this metabolite binds to HLA-B*58:01 much stronger than allopurinol, the adverse reactions are considered to be due very largely to oxipurinol.

![Figure 2. Binding mode of oxipurinol to HLA-B*58:01](image)

The structure of HLA-B*58:01 is depicted in cartoon mode, and oxipurinol in space-filling mode. The T-cell receptor approaches from the right. A cross-eyed stereoscopic drawing.

The binding mode of oxipurinol at the antigenic-peptide binding cleft of HLA-B*58:01 is shown in Figure 2. Oxipurinol is bound deeply at the antigen-binding cleft of HLA-B*58:01. Recently, the binding mode between a nucleoside reverse transcriptase inhibitor abacavir and HLA-B*57:01 was determined by X-ray analysis [3]. In this case, abacavir bound deeply at the
antigen-binding cleft induces loading of novel self-peptides into HLA-B*57:01 which results in HLA-associated drug hypersensitivity. Since oxipurinol is also bound at the antigen-binding cleft as abacavir, it is highly possible that oxipurinol alters the peptide repertoire in HLA-B*58:01 leading to IDT.

The binding affinities of six impurities except A are higher than that of oxipurinol. The possibility of involvement of the impurities in the HLA-associated adverse effect should be low because each impurity cannot exceed the limit of 0.2% according to the standard of USP [5]. However, the present results strongly indicate that the concentrations of impurities with significantly high affinity for HLA-B*58:01 such as impurity (E)-F should be strictly monitored in order to avoid IDT.

Supplements

Supplemental data are available at: http://cbi-society.info/supplement/10.1273/cbij-16-1/

References


