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Research Article

Affinity of HIV-1 antibody 2G12 with monosaccharides: A theoretical study based on explicit and implicit water models

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ABSTRACT

In order to develop potential ligands to HIV-1 antibody 2G12 toward HIV-1 vaccine, binding mechanisms of the antibody 2G12 with the glycan ligand of D-mannose and D-fructose were theoretically examined. D-Fructose, whose molecular structure is slightly different from D-mannose, has experimentally shown to have stronger binding affinity to the antibody than that of D-mannose. To clarify the nature of D-fructose's higher binding affinity over D-mannose, we studied interaction between the monosaccharides and the antibody using ab initio fragment molecular orbital (FMO) method considering solvation effect as implicit model (FMO-PCM) as well as explicit water model. The calculated binding free energies of the glycans were qualitatively well consistent with the experimentally reported order of their affinities with the antibody 2G12. In addition, the FMO-PCM calculation elucidated the advantages of D-fructose over D-mannose in the solvation energy as well as the entropic contribution term obtained by MD simulations. The effects of explicit water molecules observed in the X-ray crystal structure were also scrutinized by means of FMO methods. Significant pair interaction energies among D-fructose, amino acids, and water molecules were uncovered, which indicated contributions from the water molecules to the strong binding ability of D-fructose to the antibody 2G12. These FMO calculation results of explicit water model as well as implicit water model indicated that the strong binding of D-fructose over D-mannose was due to the solvation effects on the D-fructose interaction energy.

1. Introduction

In physiological systems, a large variety of biological functions are regulated by various interactions between biomolecules. Aiming for the understanding of the functions as well as drug developments, it is necessary to investigate biochemical mechanisms of the interactions that trigger a disease. It is known that the interaction between saccharides and their receptors is involved in many biological systems especially in viral infection (Smith and Helenius, 2004), e.g., influenza virus hemagglutinin–saccharides interaction (Gamblin et al., 2004; Skehel and Wiley, 2000; Zhang et al., 2010). The quantitative analysis of the interaction between saccharides and their receptor by theoretical calculations is challenging because of saccharides' weaker, but sensitive affinities compared with other biomolecules such as proteins or DNAs.

In the present study, we employ the fragment molecular orbital (FMO) method proposed by Kitaura et al. (Kitaura et al., 1999; Fedorov and Kitaura, 2007a). FMO method enables us to evaluate the physical properties of fragments as well as the interaction between them (Fedorov and Kitaura, 2007a). It is also possible to examine the binding affinity between a ligand and its receptor based on chemical fragments. These days, various investigations of ligands' interaction with proteins in large biochemical systems have been reported using FMO method (Fukuzawa et al., 2006; Ito et al., 2008; Yamagishi et al., 2010; Ozawa et al., 2011; Nomura et al., 2012), which are summarized in reviews (Fedorov and Kitaura, 2007a; Gordon et al., 2012). With regard to saccharides–protein interaction, FMO calculations on charged saccharides with influenza hemagglutinin (Iwata et al., 2008; Sawada et al., 2007, 2008; Takematsu et al., 2009) and a neutral high-mannose ligand complex with griffithsin (Nagata et al., 2012) were recently reported.

For the application of calculations to biochemical target, it is important to properly consider solvent effects. Among various continuum solvation models, the polarizable continuum model (PCM) (Tomasi et al., 2005) is one of the most widely used ones. The FMO-based PCM was introduced for the energy by Fedorov et al. (2006) and various enhancements of the FMO-PCM method, such as gradient (Li et al., 2010) and pair interaction energy decomposition analysis (PIEDA) (Fedorov and Kitaura, 2012), have been developed.

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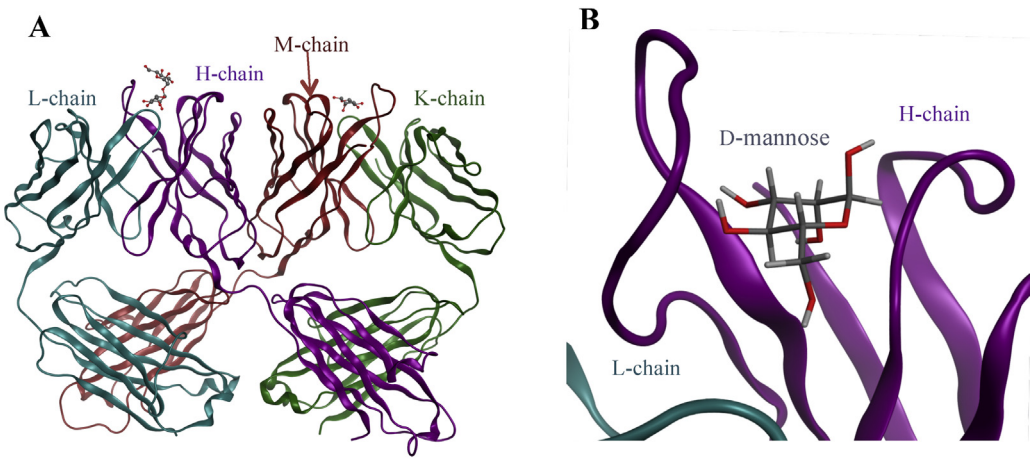

Fig. 1. Antibody 2G12–glycan complex and ligand structures (PDB ID: 1OP3). (A) Fab 2G12–mannose complex; (B) D-mannose bound to Fab 2G12.

In 2010, Sawada et al. performed the FMO-PCM calculations at the MP2/6-31G* level to disaccharides complexes with influenza virus hemagglutinin resulted in good agreement with the experimental binding energies (Sawada et al., 2010a, 2010b; Sawada, 2012).

HIV infection is a target system of our research, where an interaction of saccharides–protein plays a key role in the infection. In order to elucidate the nature of glycan–protein binding at the molecular level toward the contribution to the medications, we studied monosaccharides bound with the antibody involved in HIV-1 infection system by FMO calculations.

HIV-1 infection is the etiologic cause of Acquired Immune Deficiency Syndrome (AIDS) and has been investigated since the virus was recognized 30 years ago. At the end of 2010, UNAIDS (Joint United Nations Programme on HIV and AIDS) reported that an estimated 34 million people were living with HIV worldwide and the number of people dying of AIDS-related causes was 1.8 million (AIDS Epidemic Update, 2012). An effective vaccine is, therefore, paramount to combat the epidemic.

A remarkable feature of HIV is the dense glycan array that surrounds the exposed envelope antigens. The envelope protein gp120 of HIV-1 is one of the most heavily glycosylated proteins in nature, with many of high-mannose type glycan (Morelli et al., 2011). The glycan epitope of gp120 has been considered as potential antigenic targets for the development of an antibody-based HIV-1 vaccine.

The human monoclonal antibody 2G12 is capable of recognizing sugars on the high-mannose carbohydrate of gp120 with high affinity (Calarese et al., 2003). In 2003, Calarese et al. solved X-ray crystal structures of Fab region of 2G12 and its complexes with the disaccharide Manα1-2Man (Fig. 1) and the high-mannose oligosaccharide $Man_9GlcNAc_2$ (Calarese et al., 2003). Their study indicated the importance of the oligomannose D1 arm in the interaction between gp120 high-mannose and 2G12 (Calarese et al., 2003, 2005). Antigens that resemble these natural high-mannose epitopes of 2G12 would be highly desirable components for an HIV-1 vaccine.

In 2010, Davis and his co-workers reported X-ray crystal structures of Fab 2G12 with D-fructose (Doores et al., 2010). They also found that D-fructose had higher affinity with 2G12 than self glycan D-mannose (Doores et al., 2010). From a structural point of view, they investigated the effects of C-5 hydroxyl group of D-fructose on the ligand binding as well as water molecules in the vicinity of the binding site found in the X-ray structure. This non-self glycan could be an important component of a carbohydrate anti-HIV-1 vaccine. Therefore, the understanding of the glycans' binding mechanisms of the antibody 2G12 is critical in developing HIV-1 vaccines.

Details of the antibody–neutral carbohydrate ligand interaction are still unclear. To investigate the glycan ligand binding mechanisms of 2G12, we have shown the physicochemical picture of the interaction between 2G12 and its high-mannose $Man_9GlcNAc_2$ ligand (Koyama et al., 2013). We herein report the binding free energies of neutral monosaccharides, D-mannose and D-fructose, with HIV-1 antibody 2G12 using FMO-PCM calculations at the MP2/6-31G* level. This is the first application of the FMO-PCM calculations to the HIV-1 system where human HIV-1 antibody 2G12 binds to its ligand saccharides. From an aspect of the saccharide–protein interaction, the higher-level calculation considering solvation effects would be necessary for the appropriate evaluation of this neutral monosaccharids' moderate interaction. For this objective, explicit water molecules detected in the X-ray structure were also examined extensively by means of pair interaction energy analysis.

2. Computational details

2.1. FMO calculation in the gas phase

To elucidate the nature of a higher binding affinity of D-fructose over D-mannose, we carried out FMO calculation utilizing X-ray crystal structures of the Fab 2G12–D-fructose/D-mannose complexes as calculation models. At first we cut out the ligand-binding site from the original X-ray crystal structure in order to reproduce systems with minimum computational loads. The model used in the present study consists of peptides of a binding region of the antibody 2G12 (L-chain Val2-Val110, H-chain Glu1-Lys117) with one monosaccharide ligand. Hydrogen atoms were subsequently added to the model by means of MOE Protonate 3D program under the experimental condition; pH 7.0 and $T = 300$ K (MOE (The Molecular Operating Environment) Version 2009.10). All the protonated states of histidines of D-mannose–antibody complex (PDB ID: 1OP3) and of D-fructose–antibody complex (PDB ID: 3OAY) were same except H32; positively charged H32 (with hydrogen atoms on the δ and ε nitrogens, with D-mannose) and neutral H32 (with a hydrogen atom on the δ nitrogen, with D-fructose). This difference mainly aroused from the position as well as the direction of the hydroxyl group of the mannose (Figs. 3 and 4).

Regarding the glycan ligand, the crystal structure of Fab 2G12 with D-fructose (PDB ID: 3OAY, Resolution 1.95 Å) was utilized for the D-fructose–antibody complex model. The model for D-mannose–antibody complex was prepared using mannose disaccharide–Fab 2G12 complex crystal structure (PDB ID: 1OP3, Resolution 1.75 Å). The ligand mannose disaccharide was cut into monosaccharide D-mannose and protonated without any other refinement for X-ray structure. Using the software Facio (Suenaga, 2008), the peptides of Fab 2G12 proteins were fragmented into mono amino acid residue-fragments, except Cys-S-S-Cys