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Computational and statistical study on the molecular interaction between antigen and antibody

Tomonori Osajima, Masaaki Suzuki, Saburo Neya, Tyuji Hoshino*

Graduate School of Pharmaceutical Sciences, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8675, Japan

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ABSTRACT

Monoclonal antibodies are one of the most successful bio-molecules utilized in the clinical scene of today. It is important to clarify general characteristics of the interaction between antigen and antibody and to draw a guide for enhancing their binding affinity in rational design of antibody drugs. In this study, we carried out molecular dynamics simulations for 20 kinds of antigen–antibody complexes. From the statistical analysis of the calculation results, the following findings were deduced. At complementarity determining regions (CDRs) of the antibodies, the rates for the presence of serine (Ser) and tyrosine (Tyr) are high. The amino residues involved in direct hydrogen bonds between antigens and antibodies were examined by counting the numbers of the hydrogen bonds from the respective residues. The contribution of Tyr to the direct hydrogen bonding was the highest and that of Ser was the fourth. Furthermore, the short-distance hydrogen bonds, which is assumed to be so-called "low-barrier hydrogen bond", were observed at CDRs in three complexes. Interestingly, Ser is involved in the short-distance hydrogen bonding in two cases out of the three. This result suggests that these two unchanged polar amino acid residues play an important role for recognition of antigen. In almost all of the complexes (18/20), the contribution of the electrostatic energy (ΔE_{ele}) to the binding free energy was calculated to be larger than that of the van der Waals energy (ΔE_{vdw}). This dominance of the electrostatic energy is in contrast to the case that low molecular-weight compounds are bound to their targets. The findings of this study will be helpful to design an antibody with a high specificity and a high affinity to the antigen.

1. Introduction

Antibodies occupy an important position in biochemical research, diagnosis, and therapy, in recent years [1,2]. Regarding therapeutics, the contribution of antibody is increasing and nowadays antibody drugs account for one third of all newly approved medicines for cancers, arthritis, asthma, psoriasis, virus infection, transplant rejection, and so on [3–5]. Antibodies are a family of glycoproteins which are specifically bound to the respective antigens. The most remarkable feature of the antigen–antibody interaction is the high specificity and high affinity [6–9]. A binding strength between an antigenic determinant in an antigen (epitope) and an antigen-binding site in an antibody (paratope) is regarded as affinity. The functional strength in combining of antibody with a target protein is termed as avidity. Avidity is a measure of the overall strength of binding of an antigen with many antigenic determinants and multivalent antibodies.

One natural antibody, typically immunoglobulin, has at least two antigen-binding sites. The antigen binding site is usually formed by six polypeptide segments which consist of three variable loops of light chain (L1, L2, and L3) and three variable loops of heavy chain (H1, H2, and H3) [6,7,10]. These six loop segments are highly variable and are named as complementarity-determining regions (CDRs). The local conformational changes called as the induced fit are often observed both for antibody and antigen in their complex, suggesting that the induced fit is important for high specificity and affinity in the antibody–antigen interaction [6].

Lots of three-dimensional structures of the antigen–antibody complexes have already been determined by X-ray crystallographic analysis for a variety of antigen–antibody combinations. In this study, twenty kinds of crystal structures of antigen–antibody complexes were picked up for the computational analysis. In the choice of the twenty complexes, we avoided such crystal structures that antigen part was a linear short peptide or the resolution of X-ray diffraction was not fine. The proteins selected as antigens are influenza virus neuraminidase [11–13], human immunodeficiency virus type 1 (HIV-1) capsid protein [14,15], Taq DNA polymerase [16], hen egg-white lysozyme [17–28], anti-idiotopic

* Corresponding author. Tel.: +81 43 226 2936; fax: +81 43 226 2936.
E-mail address: hoshino@chiba-u.jp (T. Hoshino).

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Table 1
Profiles of antigen and antibody for 20 complexes used in the present MD simulations.

PDB code	Antigen	Antibody	Reference
1A14	Influenza virus neuraminidase	NC10	11, 12, 13
1AFV	HIV-1 capsid protein	Fab 25.3	14, 15
1BGX	Taq DNA polymerase (TaqP)	TP7	16
1DQJ	Hen egg-white lysozyme (HEL)	HyHEL-63	17, 18
1DVF	Anti-idiotopic antibody (E5.2)	D1.3	29, 30
1FJ1	Outer surface protein A (OspA)	LA-2	31, 32
1H0D	Human angiogenin (ANG)	Fab 26-2F	33
1IGC	Streptococcal Protein G	Mouse IgG1κ (MOPC21) Fab	34, 35
1IQD	Factor VIII	BO2C11	36, 37
1JPS	Tissue factor	D3H44	38, 39
1KB5	Mouse T-cell receptor (TCR)	Désiré-1 Fab	40, 41
1NDG	HEL	HyHEL-8	19, 20, 21
1NDM	HEL	HyHEL-26	22, 23
1NL0	Factor IX	10C12	42, 43
1UA6	HEL	HyHEL-10	20, 24, 25, 26
2JEL	Histidine-containing phosphocarrier protein (HPr)	Jel42	44, 45
2VIR	Influenza virus hemagglutinin (HA)	Fab	46, 47, 48
2VIS	HA	Fab	46, 47, 48
2VIT	HA	Fab	46, 47, 48
3HFL	HEL	HyHEL-5	27, 28

antibody [29,30], outer surface protein A [31,32], human angiogenin [33], streptococcal protein G [34,35], factor VIII [36,37], tissue factor [38,39], mouse T-cell receptor [40,41], factor IX [42,43], histidine-containing phosphocarrier protein [44,45], and influenza virus hemagglutinin [46–48] as listed in Table 1. These broad examples will provide us the information of epitope, paratope, specificity, affinity, thermodynamic property for the binding interaction between antigens and antibodies.

X-ray crystal structures, however, do not fully satisfy our understanding on the energetic aspect of the binding interaction, for example, van der Waals potential energy, electrostatic energy, and/or contribution of water molecules. Computational study enables us to examine the inter-molecular interaction between proteins, chemical compounds, lipids, ions and so on [49]. Molecular dynamics (MD) simulation is one of the major computational approaches for analyzing the interaction between epitope and paratope and the simulation can predict even a suitable epitope inducing immunological response [49,50]. Now it is important to clarify the general features of the interaction between antigen and antibody in the structural and energetic viewpoints, which will be very helpful to make a strategy to develop a new potent antibody with a high specificity and a high affinity.

The objective of this study is to clarify the dominant factors for the interaction between antigen and antibody. In this study, we performed MD simulations for twenty kinds of antigen–antibody complexes and calculated (i) the averaged three-dimensional structure and root mean squared deviation (RMSD), (ii) the appearance rate of each amino acid residue at CDR to find what amino acid residues are strongly involved in the antigen–antibody binding, (iii) the binding free energy and its energetic components in the antigen–antibody interaction, (iv) the number, distance, and angle of the direct and water molecule-mediated hydrogen bonds at CDR to characterize the hydrogen bonding, (v) the averaged B-factor values of the main chain atoms to examine the flexibility of antibody due to the binding to antigen.

2. Methods

2.1. Construction of computational model

Three-dimensional structures of the antigen–antibody complexes used in this study were extracted from the X-ray crystallographic data in the protein data bank (PDB). The respective PDB codes are 1A14, 1AFV, 1BGX, 1DQJ, 1DVF, 1FJ1, 1H0D, 1IGC, 1IQD, 1JPS, 1KB5, 1NDG, 1NDM, 1NL0, 1UA6, 2JEL, 2VIR, 2VIS, 2VIT and 3HFL (Table 1). The initial structure of each calculation model was constructed from the atom coordinates of the crystal structure with a modification by adding the missing residues and generating hydrogen atoms. Each complex model was placed in a rectangular periodic-boundary box and solvated with 15,000–60,000 TIP3P water molecules using leap module of AMBER11 program package [51].

2.2. Calculation condition for MD simulation

MD simulation was performed with sander module of AMBER11 program [51]. AMBER ff03 force field was applied. MD simulation was executed in three steps of minimization, heating, and equilibration. Atom geometry was energetically minimized in the first step. The minimization was performed with the steepest descent method for the earlier 3000 cycles and with the conjugated gradient method for the later 10,000 cycles, with only water molecules permitted to move freely. Subsequently, the minimization was performed again in a similar manner without any positional constraint on the atoms [52]. In the heating, the temperature of the calculation system was gradually increased to 300 K in the NVT ensemble condition. Then, the equilibration calculation was performed in the NPT ensemble condition with a temperature of 300 K and a pressure of 1 atm. A periodic boundary condition was applied to all the *xyz*-directions, and the pressure and the temperature were kept constant. The cutoff distance for van der Waals and Coulomb forces in a real space was set to 12.0 Å. The particle mesh Ewald method was applied to estimate the influence of long-distance electrostatic force. For all of the twenty complexes, 8 ns MD simulation was carried out and the trajectory for the last 1 ns was collected for analysis. Snapshot structures were extracted from the trajectory every 10 ps in order to analyze the average structure, the interaction energy, hydrogen bonding, atom fluctuations.

2.3. Analysis of simulation data

The average structure of each complex was calculated using a trajectory acquired every 10 ps for the last 1 ns of the simulation. All the twenty structures were visualized with PyMOL [53]. The calculations should be sufficiently equilibrated for the sake of reliable analysis. The root mean square deviation (RMSD) is one