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Antibody Druggability

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1. Introduction

We here propose the revised procedure of structural classification of the third complementarity-determining regions (CDRs) in antibody, and also propose a novel concept of "antibody druggability", an appropriate indicator of antibody evaluation.

Antigen binding site of antibody is composed of six CDRs. The five CDRs (CDR-H1, H2, L1, L2, and L3) have a limited number of canonical structures and can be identified from their amino acid sequences[1]. In contrast, CDR-H3 shows substantial diversity in length, sequence, and structure, and it has no canonical structure. CDR-H3 lies in the center of antigen-binding site and plays the most important role in the antigen recognition. We previously proposed a series of "H3-rules" designed to establish a classification system for the CDR-H3 structure based on its amino acid sequence[2,3]. Many researchers have incorporated them in antibody modeling protocols. Following proposals of these rules, the number of antibody structures being experimentally determined has increased significantly. Here, we examined the structures of CDR-H3 and L3, and revised H3-rules[4] and proposed a new classification system for CDR-L3 structures[5]. We then applied them to antibody drug sequences, and found the common structural features of CDRs in antibody drugs.

2. Method

All antibody structures having heavy and light chains available from PDB were prepared at resolutions of 2.80 Å or better. The structures with the highest resolution of each antibody were selected as representatives of free and complex structures, respectively. When more than one structure of the same high resolution was available, structures with the best R-factors were selected. Consequently, we obtained 314 antibody structures as nonredundant dataset. Our previous H3-Rules were applied to the sequences from the dataset, and the predicted structures were compared with the corresponding crystal structures. We also examined CDR-L3 structures. Structural inspection was carried out by using the UCSF Chimera graphics software. New classification systems proposed in this study were applied to 12 antibody drugs, whose sequences were obtained from DrugBank and, 1525 nonredundant antibody sequences which include both heavy and light chains were obtained from KabatMan.

3. Results and Discussion

  The structures of CDR-H3 are generally divided into two regions, "base" and "β-hairpin," which are proximal and distal to the framework regions, respectively. The bases are divided into two major forms: extended base (E), which forms normal anti-parallel β-strands, and kinked base (K), which contains a β-bulge at the second last residue of CDR-H3. H3-rules are composed of four rules, and the most important rule (rule i) judges the base form[2,3]. The following rules classify the detail structures of base form, predict the existence of hydrogen bonding ladder, and that of typical b-turn. Here, our classification of many experimentally determined antibodies following careful analysis of their sequence and structure has led us to revise our original H3-rules[4]. Our observations showed that, in many cases, the exceptions to the original H3-rules for base identification could be explained by the effect of the bottom of the antigen-binding site, the β-hairpin stability, and the interactions with environmental residues. Use of the new H3-rules yielded an increase in success ratio for the prediction of base form from 84.9 to 89.7% compared with the previous rules. We also performed systematic analyses of the CDR-L3 structures, and found novel canonical structures, and we also classified a previously identified canonical structure into two sub-types[5]. In addition, we found that two differently defined canonical structures in the κ and λ sub-types can be classified into the same canonical structure.

  We applied the new H3-rules and new canonical theory of CDR-L3 to the antibody drugs. The lengths of CDR-H3 region are less than or equal to 13 residues, and their structures were predicted to take K forms, and six of them to form hydrogen bond ladders or typical turn conformations. Almost all of the CDR-L3 structures of antibody drugs were predicted to belong to type 1 canonical structure which contains Pro residue at L95. K form is considered to be more stable than E form because of the existence of stable hydrophobic bottom of antigen binding site. Compared with the general antibodies, the CDR-H3 segment of antibody drugs is considered more stable and rigid, possibly due to requirements during production for uniform quality and rigidity to maintain a steady form for specific antigen recognition. These common features of antibody drugs enabled us to make a novel concept of antibody druggability[4]. Currently, the druggability of small compounds is measured as a suitable indicator for lead compounds evaluation during drug discovery. Similarity, antibody druggability would be an appropriate indicator of antibody design and evaluation, ultimately leading to improved success in antibody drugs development.

References
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