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氏名	黒田大祐（くろだだいすけ）
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学位論文名	Antibody Structure Analysis and Prediction for Computational Design （計算機による抗体立体構造解析と構造予測手法の開発）
論文審査委員	（主査） 教授 中村 春木 （副査） 教授 中川 敦史　招聘教授 水口 賢司

論文内容の要旨

Antibodies are the one of the most important therapeutic compounds. Recent clinical trials using antibodies with the low toxicity and high efficiency have been raising expectations for the development of more potent antibody drugs. However it remains difficult to obtain a suitable therapeutic antibody only with experimental approaches. This thesis would contribute to the progresses in the field of computational antibody drug discovery, mainly focusing on antibody structure modeling. Many attempts have been made for modeling CDRs from the sequence, which had revealed the limited number of conformations of antigen-binding site, called canonical structures (other than H3). Much more efforts have been made on CDR-H3, which plays an important roll in antigen recognition. Knowledge-based rules were derived from crystal structures in the Protein Data Bank to classify CDR-H3. Further computational methods could be used in drug discovery based on the homology models, including epitope predictions, protein-protein docking and energy calculations with approximate potential functions. These methods should guide experimental studies to improve the affinities and physicochemical properties of antibodies.

My goal is to design antibodies using computer. Toward this end, the aim of this thesis is twofold: 1) Understand the structural determinants and energetics of antigen-binding sites or canonical structures and 2) develop the prediction method of antibody structures from the amino acid sequences. Therefore, first, I have refined conventional classification rules for hypervariable loops in antibodies. During the analyses and the classifications, I have developed an antibody structure database, called *Ig-Base*, based on the Relational Database Management System (RDBMS). I also carried out energy-based loop predictions, which suggests that the protein environment is the major determinant of antibody canonical structures of CDR-L3 rather than the loop sequence itself. This implies that CDR-L3s wouldn't assume non-canonical conformations even when the conventional "key" residues are not conserved, and the canonical structures are essentially stable conformations. Then, putting all of this together, I have developed an antibody modeling system using fragment assembly, state-of-the-art knowledge-based rules, and energy-based optimization. I showed that current PDB-based loop modeling protocol is sufficiently accurate to construct a loop structure with less than 12 residues length and the main problem of protein loop predictions is the scoring part rather than the sampling. Insight gained from this thesis would be useful for computational antibody design and engineering.

論文審査の結果の要旨

抗体は、生体外からの異物(抗原)を特異的に認識し、生体防御機構を担う重要な蛋白質である。抗体の特異的な抗原認識機構の理解は、単に医学・生物学のみでなく、薬学・農学・工学分野での応用に果たす役割も大きい。また、近年抗体が持つその特異性が注目され、抗体を医薬品として応用する抗体医薬が世界中で開発されている。申請者はこの2つの課題に構造バイオインフォマティクス及び計算科学の手法を用いて「抗体の立体構造予測」という視点から、特に抗体の立体構造構築原理の理解を目指し、研究に取り組んできた。具体的には、多数の構造既知抗体から新たな配列-構造相関ルールを見出し、PDB中の大量のループ候補の構造を絞り込み、「抗体らしい」ループ座標のみを抽出するシステムを構築した。それにより、抗体のアミノ酸配列からの立体構造の高精度な構築が可能となった。また非経験的な蛋白質ループ予測手法を用いることで、抗原認識部位の構造構築原理を見出し、抗原認識部部位の立体構造は、そのアミノ酸配列によるローカルな力だけではなく、周囲の蛋白質環境もその構造に影響を与えている可能性を示した。経験的な構造予測手法と非経験的な手法を組み合わせることで、抗体の立体構造に関する理解を深める内容であった。研究と発表内容を総合的に判断すると、申請者が学位を受けるに値するものと認める。