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Editorial Open Access

Approach to Structure-Based Drug Discovery on Molecular Biology

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Editorial

Biophysical Chemistry has made remarkable advances in combination with the technological advances in Molecular Biology, in which the recombinant DNA manipulation has allowed researchers to obtain a large quantity of protein and DNA enough to understand fundamental aspects of biological phenomena and structures. Especially, the three dimensional structures of protein, DNA, and enzyme-inhibitor complex have been determined by using the nuclear magnetic resonance (NMR) spectroscopy and the X-ray crystallography, leading to an accumulation of structural data of the biomolecules. The resource including biological macromolecular information about the individual atomic coordinates help researchers understand all aspect of molecular function, mechanism, and pathways in detail and also develop a medicine in pharmaceutical science.

NMR is known to be a well-established method for determining protein structures, as well as to be a sensitive method for detecting the binding of small compounds to proteins. The NMR resonances of ligand and target observed are useful for screening drug candidates [1]. Especially, the detection of ligand binding using the two dimensional experiment, heteronuclear single quantum coherence (HSQC), is reported to be successful [2,3]. The Structure Activity Relationship (SAR) by NMR [2] is a practical approach using the HSQC experiment in which some molecular fragments binding to target are screened, followed by optimization of fragments for better binding to target and/or design of linker to connect the optimized fragments. In order to facilitate both optimization and design, the Fragment-based Drug Discovery (FBDD) has been exploited in both academia and industry [4], in which the three-dimensional structures stored in the data base are frequently employed to both establish the binding manner and facilitate the optimization. This structure-guided optimization leads to the drug discovery. This FBDD method can be extended as large as 100 kDa macromolecules in which a kind of amino acid is selectively replaced with the labeled one [5].

In addition, an NMR difference experiment, called as saturation transfer difference (STD), is also reported to be realistic for screening [1]. In order to screen ligand candidates, the frequency selective pulse that excites target resonances is applied to a mixture of a target and a set of ligand candidates, in which the saturation that arises from selectively exited nuclei in the target molecule is transferred to the ligand sites specifically binding to target through intramolecular cross relaxation pathways. This experiment is called as an on-resonance experiment. The signal intensity of resonances observed in the on-resonance spectrum can be subtracted from that of the off-resonance spectrum that is obtained by using a pulse sequence without the frequency selective pulse. The STD response is the spectral difference by which a ligand binding to target is sorted out from ligand candidates.

We have been engaged in some different kinds of protein research, including the structural change of nucleosome, the catalytic mechanism of enzyme, and the interaction between drug and protein, in which different types of technologies in Molecular Biology have been used. We believe that these technologies combined with the NMR methods described above lead to an efficient drug discovery. For example, the nucleosome that is a large macromolecule target in detecting NMR signals may be attractive. The nucleosome, which is widely known as a basic repeating unit of chromatin formation through which DNA packaging is achieved in eukaryotic nuclei, consists of 147 base pairs of DNA wrapped in 1.7 left-handed super helical turns around the surface of an octameric protein core. This core is formed from two copies each of the four core histones: H2A, H2B, H3, and H4. The histones are subjected to a variety of post-translational modifications including acetylation, phosphorylation, methylation, ubiquitination, and ADP-ribosylation. All of them, which are tightly related to cell functions, are expected to be controlled by drugs *via* the regulation of structural change of nucleosome. However, considering an analysis in which biophysical methods are applied to detect a signal of nucleosome, there is a problem associated with their modifications because the use of such histone proteins extracted from living cells is predicted to cause undesirable effects on the nucleosome. In order to solve this problem, the nucleosome reconstituted from unmodified recombinant histones that are synthesized in the prokaryote *Escherichia coli* can be used. Actually, we have made such kind of nucleosome to detect a structural change by using CD spectroscopy [6]. Drug discovery related to the nucleosome research is one of the challenges for us. The amino acid-selective labeling may be a pivotal method for realizing the challenges. One of them, a structural investigation using NMR methods in combination with ^{15}N-histidine selective labeling contributes to understanding the mechanism of CO_2 hydration reaction catalyzed by carbonic anhydrase (29.3 kDa) [7]. In addition, the ^{13}C-ligand labeling contributes to understanding the interaction of carbonic anhydrase and acetazolamide [8].

The number of drug candidates a target molecule has been estimated to be 10^{40} [8]. It is difficult that a randomly screening approach (even when High-throughput screening (HTS) is used) is applied to more than 10^6 compounds, owing to the limited experimental capability [4]. Here, a development of Structure-based Drug Discovery in combination with Molecular Biology is the major challenges for researchers [9].

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