1. Introduction

Nuclear magnetic resonance (NMR) is a physical phenomenon based on the magnetic properties of atomic nuclei oriented by a strong magnetic field. Currently, NMR is not only an indispensable tool for chemists but also has widespread biological, clinical, and industrial applications. In particular, modern high-resolution NMR spectroscopy provides us with information on molecular structure, motion, and interaction even with biological macromolecules such as proteins. The NMR information is provided as spectral ‘peaks’ originating from the individual atoms in the molecules.

Its ability to elucidate three-dimensional (3D) structures of complicated protein molecules and their complexes makes NMR spectroscopy one of two major methodologies in the structural genomics projects, along with X-ray crystallography. In the past five years, such projects endeavored at determining the atomic coordinates of proteins in the living systems in a comprehensive manner. Indeed, recent revolutionary advances in biomolecular NMR spectroscopy have made possible the high-throughput determination of 3D structures of simple proteins, given their sizes are sufficiently small. It is expected that the accumulating protein NMR data provide the structural basis of physiology and diseases and also offer clues for rational drug discovery and design.

2. Current challenges in biomolecular NMR spectroscopy

Although the systematic NMR methodology has been established for structural analyses of small simple proteins, there still exist various problematic biomacromolecules confronting NMR analyses. For example, larger proteins are obviously more difficult to treat because they exhibit innumerable peaks severely overlapping one another in the charts.
which hamper detailed spectral analyses. In addition to this difficulty, the slower molecular tumbling of the larger proteins in solution cause the broadening of NMR peaks, rendering them barely detectable. Unfortunately, medicinally important membrane proteins as putative drug targets belong to this hard class of molecules.

Another difficult subject is the structural analysis of glycoproteins, which are proteins modified with sugar chains. Many of the proteins in the living systems are actually not naked but wear sugar chains which mediate molecular recognition events involved in cell-cell communication as well as viral infections and also operate as varying passports of the proteins in cells. Despite the biological importance of the sugar chains, NMR analyses of these molecules are not facile because they exhibit structural heterogeneities and conformational fluctuations. The glycoproteins cannot be prepared for NMR measurements conventionally by molecular biology techniques because the sugar chains are not directly coded in the genome.

NMR spectroscopy has great potential to offer information not solely on static structures of the molecules but their dynamics at atomic level. The conformational fluctuations of biological macromolecules are thought to be relevant to their biological functions such as enzymatic action. Many structural biologists are currently interested in observing the usually hidden faces of protein molecules and transient intermediates in their assembling processes.

3. Conclusion

To overcome the current difficulties and to develop new methodologies, NMR spectroscopists indisputably need to cooperate with scientists working in other fields. For instance, the most straightforward solution to the problems arising from the low sensitivity and poor resolution is to increase the strength of the applied magnetic field. At present, an ultra-high field NMR spectrometer equipped with 21.6-tesla superconducting magnet (generating proton 920 MHz resonance frequency) is at work in our institute. Further progress is expected towards higher magnetic field NMR using high-temperature superconducting materials, which would be achieved by advances in material science. Also, frontier approaches in informatics would greatly contribute to the visualization of dynamic structures of biomacromolecules based on the NMR data. Thus, a multidisciplinary joint effort will open up a new avenue for NMR spectroscopy.

References

