

LIFE SCIENCE:



The finest X-ray beam produced from a synchrotron source is a powerful tool for protein crystallography, which reveals profound knowledge and details of structure-function relationship for extensive biological macromolecules. For adaptation to various experimental needs and requests, SPring-8 structural biology beamlines are continuously developed. Here, we present some selected reports from many fruitful results obtained this year.

One of the major expected contributions of structural analyses is the investigation of the mechanisms of diseases and biological responses to pathogeny or stress leading to the development of cure and prevention for health benefits. The structure of influenza RNA polymerase revealed the relationship between its assembly and function. Increasing dementia caused by Alzheimer's disease is a difficult problem not only for patients and caregivers but also for societies in aging populations. One of its major pathogenesis is the accumulation of an insoluble degraded protein produced by β -secretase and BACE1. The crystal structures of active and inactive forms of BACE1 reveal conformational changes during its catalytic reaction. As another marked health problem, metabolic syndrome associate with lifestyle-related diseases increases the risk for diabetes, thus its therapy is expected. Excessive nutrients are converted and stored as fatty acids. Biotin protein ligase is a key component in fatty acid synthesis and its structure reveals the activation mechanism of the synthetic pathway. These structures might be used for novel drug design.

STRUCTURAL BIOLOGY

Stress is quite common and a serious problem for living organisms. Excessive oxidation and UV radiation cause severe damage to proteins and nucleotides by chemical reaction. SoxR is a transcription factor sensing oxidative stress by its own iron-sulfur cluster. Its structure reveals that the oxidative state of the metal cluster causes structural changes to adopt DNA binding and the promotion of transcription of antioxidant enzymes. An antioxidant enzyme, peroxiredoxin, showed the novel structure of its hypervalent sulfur compound in multiple oxidation states. Such structural and functional analyses of the ancestral protein from an archaeal bacterium might reveal biological evolution in stress resistance. Melanosome is a melanin vesicle, and its maturation and storage are essential for photoprotection. The X-ray analysis of Rab27-Slac2 responsible for melanosome transport reveals the structural basis of the specific interaction between them, and might be used for drug development for Griscelli syndrome caused by transport failure.

On the other hand, structural analysis of macromolecules is also opening the profound secret of life. One key mechanism of life is signal transduction, which is essential for survival because living things must respond to environmental signal or stimulus. The signal transduction pathway starts with sensors and the signal reaches regulators via messengers. Many of the sensors located in the cell membrane receive extracellular signals and transmit the signal to intracellular messenger. G-protein coupled receptors (GPCRs) are the largest family of such proteins, and thus, are considered as the most important drug targets. Rhodopsin is the largest subgroup of GPCR receiving light photons at the retina covering the back wall of the eye. The detailed analysis of squid rhodopsin elucidates its photoactivation mechanism. Plants have no eyes but sense light for controlling development such as flowering and the growth of shoot and root. Phototropin contains a chromophore, flavin, sensing blue light and induces structural changes leading to the transmission of the signal to downstream messengers. Its structure provides clues to the signaling mechanism.

To transfer the sensed signal to messengers and regulators correctly, the molecular interaction between the components is quite essential. The analysis of the interaction by crystallography is limited because of its weak, instant and dynamic features. Small-angle X-ray scattering is an effective tool to investigate such a weak protein-protein interaction and used to reveal structural variety and flexibility in a couple of molecules, aconitase and isocitrate dehydrogenase, in a carbon metabolic pathway.

The signal that reaches transcription factors affects the expression of gene information stored in DNA. Gene expression is mediated by the activation of transcription factors and their interaction with DNA. The structural analysis of SdrP showed its similarity with a well-known transcription factor, CRP, but also the novel features of the protein. In the mechanism of DNA replication, the structure of a key protein RepE working as both a repressor and a replication initiator is determined. Observed structural changes clarify its functions and further analysis might reveal the structural relationship with signaling from DnaK system.

As a scientific topic this year, Prof. Shimomura was awarded the Nobel Prize in Chemistry for the discovery of green fluorescent protein (GFP). This is widely used as a reporter of expression and there are many variants developed. One of the variants, Dronpa, was analyzed in terms of its structure and mechanism of photochromism. This might accelerate further developments of the reporter gene.

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