Life Science:

Structural biology deals with the minutest hierarchy, composed of atoms and molecules, in biological organization. Through the 3D visualization of biomacromolecules, it reveals biomolecular functions and mechanisms as a consequence of their structural features. Among the methods of visualization, X-ray crystallography is the most powerful method, but requires good quality of macromolecular crystals. To analyze structures from ill-diffracting crystals or diverse aspects of molecular structures, synchrotron beamlines have been progressively developed. As a recent achievement of the developments at SPring-8, a micro-focus beamline BL32XU has been constructed as part of a national project, the 'Target Protein Research Program' (TPRP) and is dedicated to the analysis of protein microcrystals. We can introduce the first results gained through the use of BL32XU in this issue of Research Frontiers 2012, since beamline was established in mid-2010. The next project, the 'Platform for Drug Design, Discovery and Development,' was started in 2012. BL41XU will be upgraded by installing new optical components to produce a high-flux microbeam and a new X-ray detector for ultrafast data collection. This improvement is expected to improve the efficiency of the beamline. Overall, in the field, developments in photon and quantum beam technology are expanding structure determinations of bionanomolecules. In particular, the compact X-ray free electron laser facility, SACLA, will be establishing experimental environments for determining the structures of very tiny crystals, such as those of membrane proteins, or single particles of supramolecular complexes and organelles. Sooner than later, we will be faced with the problem of proper use of these facilities.

Within the above backdrop, many outstanding results have been reported in 2012, as summarized briefly below. Among them, those on several types of membrane transport proteins stand out. This membrane protein family is involved in the movement of ions, small molecules, or macromolecules across cell membranes. Kato *et al*. revealed the structure of channelrhodopsin. This protein is well applied to neuroscience research owing its proton-transfer function in response to light. Its molecular mechanism driven by the

Structural Biology

photoisomerization of chromophore was revealed, and it will be applied to improving this protein tool for used in research. Fujiwara *et al*. analyzed another proton channel relevant to bacterial killing by immune cells. The assembly of its membrane-transport domains, regulated by the association/dissociation of its intracellular domains that sense fever heat, induces the proton transfer that leads to the production of reactive oxygen species to kill the pest. Conversely to the two passive transport proteins, a proton pump acts actively against the concentration gradient of the portage, using chemical energy. Some of the pumps found in plants use the energy supplied from pyrophosphate instead of ATP. Lin *et al*. determined the structure of a pyrophosphate-energized proton pump and revealed unique features of this protein family. Next, two active transporters move small molecules. Sugar is a major energy source for living organisms. Sun *et al*. determined the structure of a sugar transporter strongly related to diabetes, revealing a unique mechanism of substrate recognition and opening up the possibility of drug design for the protein. Efflux transporters have been discovered in multidrug-resistant bacteria and pass out toxic antibiotics from cells. Nakashima *et al*. determined a new structure in which both large and small drug molecules are bound to two rooms of its pocket. The new findings on the efflux mechanism resembling a peristaltic pump should facilitate drug discovery to pathogenic bacteria.

Five important biological molecules in other categories were selected. Alzheimer's disease (AD) is caused by the accumulation of a certain peptide into cells, induced by a mutation of a membrane protease, preseniline. Dang *et al*. solved the structure of its homolog and showed the unique architecture of the protein family. This is an important clue in resolving the mechanism of AD. Next, Mizushima *et al*. unraveled the structure of a bacterial toxin that weakens the host cell response to a dysentery bacterium. Its structural analysis showed the presence of a protease-like active center, resulting in revealing the mechanism behind the suppression of the host's response. Dynein is a motor protein that walks on the cellular skeleton to transport large molecules. The high-resolution structural analysis of dynein by Kon *et al*. unveiled the molecular mechanism of protein walking. Histone is essential to package and order DNA, whereas CENP proteins appear in the unique kinetochore structure during cell division and repackaging of DNA into daughter cells. Nishino *et al*. determined the structures of CENP protein complexes and showed unique DNA binding modes even in structures similar to those of histones. An RNA fragment, piRNA, bound to Piwi proteins maintains genome integrity in germ line cells, but the mechanism of its production remains unknown. Nishimatsu *et al*. proposed a new model of piRNA biogenesis by determining the structure of an RNase, Zuc.

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