Laboratory of Molecular & Structural Biology

Graduate School of Science

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The cells that make up our bodies contain an efficient "mass transport system" that supplies necessary items to the necessary places at the necessary times, and this function is essential for biological activities. Our laboratory aims to elucidate the molecular mechanisms of intracellular material transport and logistics by both structural analysis at the atomic level and functional analysis at the single molecule level. Recently, we have been focusing on the mechanism of the operation of "dynein," a giant protein nanomachine that plays an important role in the transport of substances in the cranial nervous system, and we have succeeded in determining its atomic structure.

What is an intracellular transport system?

Within the cell, a wide variety of macromolecules, including proteins, are in thermal motion at a rapid rate of several meters per second. However, because the direction of thermal motion is random, it is not effective for long-distance transport in a specific direction. For example, in a one-meter long neuron, it takes more than 100 years for a standard-sized protein molecule to reach the nerve terminal from the cell body by thermal motion. Eukaryotic cells have successfully addressed the long-distance transport problem by establishing a protein system that actively transports materials. This transport system supports a wide range of fundamental biological processes such as intracellular trafficking, cell division, and cell migration, and even partial defects in this system have been shown to cause a variety of disorders such as neurodegenerative diseases, developmental abnormalities, and infertility. Our laboratory aims to elucidate how this important intracellular transport system works at the atomic level and to understand it in the language of chemistry and physics.

Elucidation of the kinetic mechanism of "dynein," a cell-center-directed transport engine

The engine of the intracellular transport system is a group of three types of proteins called cytoskeletal molecular motors: myosin, kinesin, and dynein. Among these, the motor mechanism of dynein, which is responsible for the transport of substances toward the minus end of microtubules (generally toward the center of the cell), remains largely unresolved, despite half a century of research. We have been working to determine the atomic structure of dynein, which will be a companion to understanding the dynein kinetic mechanism. First, we established the world's first mass expression system of recombinant dynein, which is the basis for structural and functional analysis. Next, we crystallized the core region of dynein (motor domain) and analyzed it at 4.5 A resolution to clarify its structure at the secondary structure level. We have also succeeded in crystallizing the core region of dynein at 2.8 Å resolution, and have determined the atomic structure of the core region of dynein, which allows us to discuss the motor mechanism at the level of individual amino acid residues. An important issue for the future is to clarify the structural basis of how dynein molecules generate forces and move in one direction on microtubule rails. To this end, we are conducting structural studies using a multifaceted approach centered on protein crystallography and cryo-EM analysis.

Toward elucidation of intracellular substance transport

Intracellular transport systems transport a wide variety of cargo, from relatively small, nanometer-sized items such as protein complexes to large, micrometer-sized materials such as membrane vesicles, Golgi apparatus, mitochondria and nuclei in the endocytosis pathway. However, our understanding of even the basics of how specific cargoes are sorted, loaded, transported to specific locations in the cell, unloaded, and returned to their original locations is incomplete. In our laboratory, we are trying to elucidate the whole picture of the molecular mechanisms of transport, especially focusing on neuroaxonal and intraciliary transport, by integrating biochemistry, structural biology, and cell biology approaches.

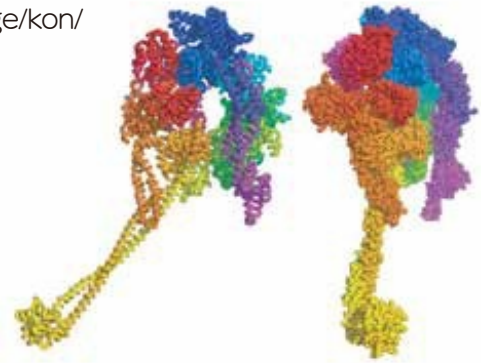

Figure 1: Atomic structure of the cell-center-directed transport engine "dynein" (Kon et al., 2012, Nature 484, 345)

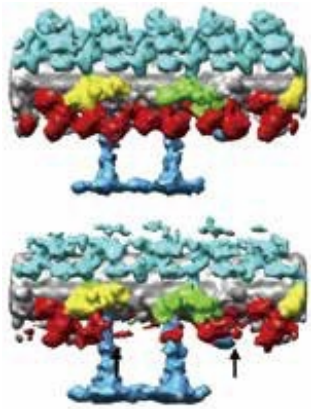

Figure 2: Axonemal structure of mutants with aberrant transport mechanisms (©2012 Bui et al. Journal of Cell Biology. 198:913-925. doi: 10.1083/jcb.201201120, modified from doi: 10.1083/jcb.201201120)

Research/life is a repetition of finding a problem to challenge, gathering information, challenging, and disseminating the results. Let's polish the foundation, gather friends, and challenge the unexplored areas of bioscience together!

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