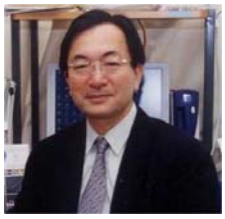
【Grant-in-Aid for Scientific Research(S)】
Biological Sciences (Biology)



Title of Project：Regulatory basis for biomotility: Chemo-mechanical feedback loop

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Research Area：Biophysics

Keyword：Biomolecular motors, Auto-oscillation of the contractile system, Cell division

【Purpose and Background of the Research】

For many years we have been studying the functions of biomotile systems, focusing on their structural and functional hierarchy. We have clarified, in particular, the existence of the mechanochemical coupling between the intramolecular load and the enzymatic activity during the movement of single molecular motors such as kinesin and myosin V. In the present project, we will focus on the intracellular movement, auto-oscillation of the contractile system of muscle, and cell division as typical examples of biological movement, and try to make clear whether the forces produced by the molecular motors play an important role in the regulation of the elementary processes of motion such as transport/oscillation/division. That is, we will show that the chemo-mechanical feedback loop (CMF loop) exists throughout the whole hierarchical organization.

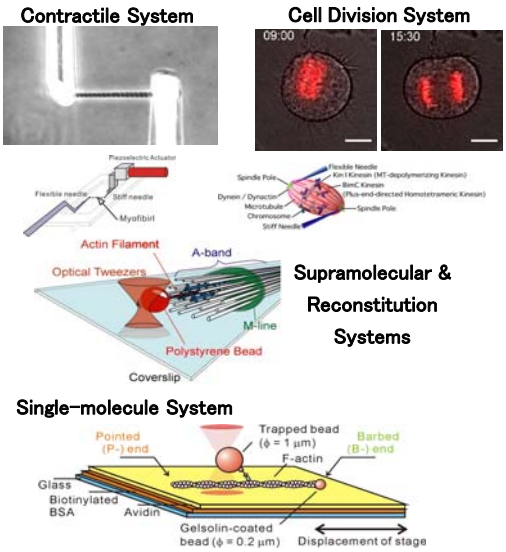
【Research Methods】

On the single-molecule level, we will examine the role of the CMF loop in the mechanisms of the motility and depolymerization/severing of cytoskeletal tracks, by measuring rupture force and determining binding mode of various myosins and regulating proteins with actin, as well as kinesins (such as MCAK) with microtubules. In the myofibrils we will focus on the molecular mechanism of the auto-oscillation (SPOC), especially in cardiac muscle, coupled with the construction of the theoretical model. Concerning cell division, we will concentrate on the balance of tension in the mechanism of chromosome segregation, perturbing it by applying external forces to the mitotic cells. This approach will allow us to confirm the existence of the CMF loop and make clear its mechanism on various levels of biological hierarchy.

【Expected Research Achievements and Scientific Significance】

To show clearly, on the molecular level, the existence of the CMF loop (acting in the direction as shown top right, as well as in the opposite direction), within the hierarchy of bio-motile systems, from single molecules and ensembles to supramolecular organizations, cells, and tissues. This will clarify the (common regulatory) mechanism of the biological motility and will possibly become a prime achievement of the biophysical research.

CMF loop: <enzymatic activity → active conformational change → force generation → passive deformation of molecules / molecular ensembles and architecture → modulation of enzymatic function>



【Publications Relevant to the Project】

"Robust processivity of myosin V under off-axis loads." Y. Oguchi, S. V. Mikhailenko, T. Ohki, A. O. Olivares, E. M. De La Cruz & S. Ishiwata (2010). *Nature Chem. Biol.* **6,** 300-305.

"Inter-sarcomere coordination in muscle revealed through individual sarcomere response to quick stretch." Y. Shimamoto, M. Suzuki, S. V. Mikhailenko, K. Yasuda & S. Ishiwata (2009). *Proc. Natl. Acad. Sci. U.S.A.* **106,** 11954-11959.

"Probing the mechanical architecture of the vertebrate meiotic spindle." T. Itabashi, J. Takagi, Y. Shimamoto, H. Onoe, K. Kuwana, I. Shimoyama, J. Gaetz, T. M. Kapoor & S. Ishiwata (2009). *Nature Methods* **6,** 167-172.

【Term of Project】 FY2010-2014

【Budget Allocation】 167,500 Thousand Yen

【Homepage Address and Other Contact Information】

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