【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project : Molecular mechanism of membrane proteins regulated by physical stimuli

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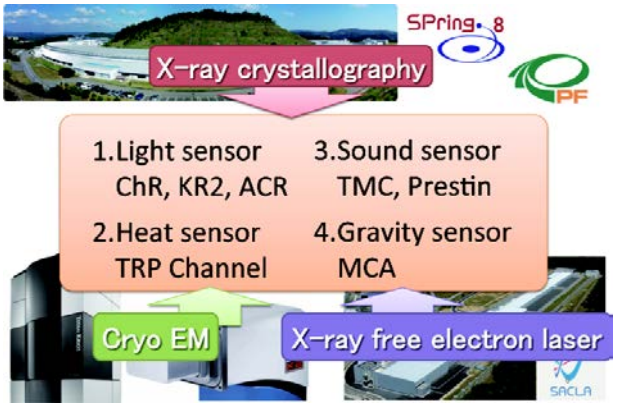
Research Project Number : 16H06294 Researcher Number : 10272460
Research Area : Structural Biology
Keyword : channel, physical stimuli, X-ray crystallography, cryo-EM, XFEL

【Purpose and Background of the Research】

We have promoted researches on channels and transporters acting as chemical sensors. In this study, based on the achievements and techniques so far, we will focus on ion channels gated by physical stimuli to elucidate structure-function relationship of physical sensor at an atomic resolution. Living organisms preceive physical stimuli such as light, heat, and sound (mechanical stress and gravity), and convert them quantally and thermodynamically into cation transport by channels, which activates neural cells and induces proper behavior of the organisms. However, the mechanisms how the physical stimuli activates physical sensor channels remains unknown. We are promoting structural and functional researches on rhodopsin-family proteins perceiving light, TRP channels perceiving heat, and TMC channel and Prestin perceiving sound to elucidate molecular mechanisms of physical sensor at an atomic resolution.

【Research Methods】

For promotion of this research, we will innovate the state-of-the-art technologies such as X-ray crystallography, X-ray free electron laser and cryo EM for structure determination, combined with dynamics analyses such as MD simulation, ESR, single molecular FRET, high-speed atomic force microscopy and functional analyses such as genetics, electrophysiology, and liposome-based analyses to elucidate structure, dynamics and function in various angles.



【Expected Research Achievements and Scientific Significance】

In addition to the traditional X-ray crystallography, we will apply pump-probe technique using XFEL to rhodopsin-family proteins to preform time-resolved structure determination, and will use cryo EM for TRP channels, TMC and prestin with large molecular weights. These analyses provide dynamics information, which will be complemented by MD simulation and *in vitro* and *in vivo* functional analyses. Furthermore, dynamics analyses using ESR, single molecular FRET and HS-AFM will allow us to integrate all the results to elucidate the whole picture of dynamic molecular mechanism of how the physical stimuli activates physical sensor channels.

【Publications Relevant to the Project】

- H. E. Kato, K. Inoue, R. Abe-Yoshizumi, Y. Kato, H. Ono, M. Konno, T. Ishizuka, M. R. Hoque, S. Hososhima, H. Kunitomo, J. Ito, S. Yoshizawa, K. Yamashita, M. Takemoto, T. Nishizawa, R. Taniguchi, K. Kogure, A. D. Maturana, Y. Iino, H. Yawo, R. Ishitani, H. Kandori and O. Nureki "Structural basis for Na^+ transport mechanism by a light-driven Na^+ pump" ***Nature 521,*** 48-53 (2015)
- H. E. Kato, F. Zhang, O. Yizhar, C. Ramakrishnan, T. Nishizawa, K. Hirata, J. Ito, Y. Aita, T. Tsukazaki, S. Hayashi, P. Hegemann, A. D. Maturana, R. Ishitani, K. Deisseroth and O. Nureki "Crystal structure of the channelrhodopsin light-gated cation channel" ***Nature*** **482**, 369-374 (2012).

【Term of Project】 FY2016-2020

【Budget Allocation】 433,300 Thousand Yen

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