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

Title of Project : Structural basis for molecular mechanisms of membrane transporters.

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Research Area : Structural Biology, Biophysics, Biochemistry, Molecular Biology
Keyword : Transporter, X-ray crystallography, Computer simulation, Electrophysiology

【Purpose and Background of the Research】

Plasma membrane defines the cellular boundary and maintains the intracellular circumstance distinct from extracellular one, which is essential for life. Membrane transporters embedded in the membrane transport various substances to maintain the cellular homeostasis. The main points of the transporter research are: (A) how the transporters drive their transport, (B) how the transporters recognize their specific substrates and (C) how the transporters regulate their transporting activities. Although full understandings of molecular mechanisms of transporters are limited due to the difficulty of their structure determination, we have gained pioneering achievements by solving the crystal structures of six transporters. Based on the achievements, our research goal is to comprehend molecular mechanisms of membrane transporters, focusing on the above three main topics.

【Research Methods】

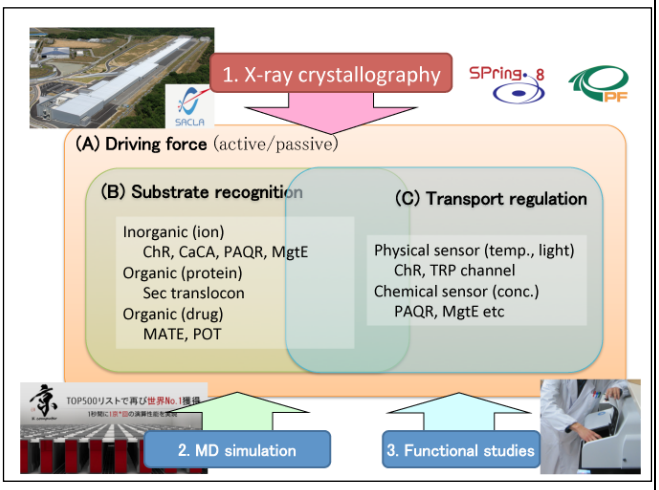

Fig. 1 Strategy

To clarify the molecular mechanisms of membrane transporters,

1. We will first determine their static structures by X-ray crystallography
2. We will then clarify their dynamic motions by MD simulation
3. We will finally verify the hypothesis derived from their structures by *in vitro*/*in vivo* functional analyses.

We will mainly focus on

1. Transport mechanisms by divalent cation transporters
2. Transport regulatory mechanism of physical sensors
3. Transport mechanisms of organic substances such as amino acids, sugars, proteins and drugs

【Expected Research Achievements and Scientific Significance】

In this project, we will take the world leadership in uncovering the comprehensive and general molecular mechanisms of membrane transporters by structural and functional studies shown in Fig. 1. Genetic dysfunction of membrane transporters often causes various diseases. Therefore, the achievements of this research not only contribute to basic science, but also to medical application such as structure-based drug design.

【Publications Relevant to the Project】

・"Crystal structure of the channelrhodopsin light-gated cation channel" H. E. Kato（12 authors） K. Deisseroth and O. Nureki ***Nature*** **482**, 369-374 (2012).
・"Structure and function of a membrane component SecDF that enhances protein export" T. Tsukazaki（8 authors） K. Ito and O. Nureki ***Nature*** **474**, 235-238 (2011).
・"Conformational transition of Sec machinery inferred from bacterial SecYE structures" T. Tsukazaki（8 authors） K. Ito and O. Nureki ***Nature*** **455**, 988-991 (2008).

【Term of Project】 FY2012-2016

【Budget Allocation】 167,600 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.nurekilab.net/