

Structural basis for molecular mechanisms of substrate recognition and transport regulation by membrane transporters

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【Outline of survey】

Membrane transporters maintain the intracellular circumstances by strictly regulating the import and export of metal ions, sugars, metabolites and drugs etc. To elucidate at an atomic resolution (A) how the transporters drive their transport, (B) how the transporters exclusively select their specific substrates and (C) how the transporters regulate their transporting activities, we will perform (1) structure determination by X-ray crystallography, (2) dynamic property analysis by MD simulation and (3) *in vivo* and *in vitro* complementary experiments, focusing on ion transporters of magnesium, iron and heavy metals, temperature-sensing cation channels, sugar transporters and multidrug transporters. Originality of this project is to uncover the essential molecular mechanism of membrane transport by comparing and integrating the functional mechanisms of transporters specific for various kinds of targeted solutes. Since Nobel prizes were awarded for investigations on aquaporin and potassium channel, more and more structural analyses of membrane transporters have been reported. In this project, we will first elucidate the three main unresolved mechanisms (A)-(C) by the above strategies (1)-(3).

【Expected results】

Plasma membrane defines the cellular boundary to maintain the distinct intra-cellular circumstances, which is essential for life. Transporters embedded in the membrane create the distinct cellular circumstances by regulating the transport of various substances. Therefore, structural and functional investigations of membrane transporters may elucidate the fundamental mechanisms of maintenance of life. Furthermore, since dysfunctions of transporter proteins are related to cardiac, renal, gastrointestinal and cranial nerve diseases, achievements of this research project may lead to medical application such as structure-based drug design (SBDD), in addition to the scientific significance.

【References by the principal investigator】

“Crystal structure of the MgtE Mg²⁺ transporter” M. Hattori, Y. Tanaka, S. Fukai, R. Ishitani, O. Nureki *Nature* **448**, 1072-1075 (2007).

【Term of project】 FY2008–2012

【Budget allocation】

159,900,000 yen (direct cost)

【Homepage address】

<http://www.x-ray.bio.titech.ac.jp/>