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

Broad Section F

Title of Project : Uncovering the secrets of lipid-transporting ABC proteins

Kazumitsu Ueda
(Kyoto University, Graduate School of Agriculture, Professor)

Research Project Number : 18H05269 Researcher Number : 10151789
Keyword : ABC proteins, cholesterol, transporter, atherosclerosis

【Purpose and Background of the Research】

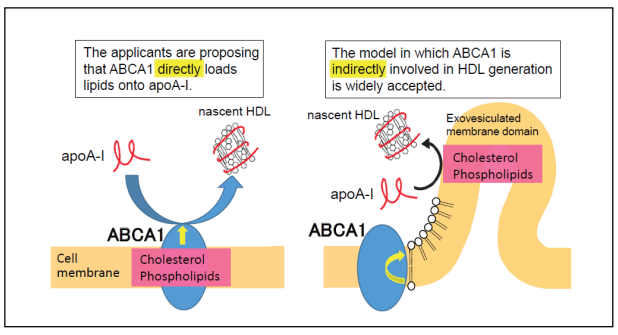
Genome analyses have revealed that 48 genes of the ATP-binding cassette (ABC) protein family are encoded on human chromosomes, and that defects in more than 20 family members are related to various diseases. Thus, ABC proteins play important roles for maintaining human health.

Ueda has been working on ABC proteins for 30 years, since the discovery of the multidrug transporter MDR1 (ABCB1), and recently succeeded in establishing a platform for ABC protein research by revealing the mechanism of MDR1 function based detailed structural analyses. In this project, we are aiming to reveal the mechanism of lipid-transporting ABC proteins, specifically ABCA1.

ABCA1 is a key transporter involved in the generation of high-density lipoprotein (HDL). However, the mechanism of HDL generation remains controversial. According to a widely accepted model for HDL generation, ABCA1 generates specific membrane domains (i.e., exovesiculated membrane domains) with outward phospholipid translocation activity, and apoA-I (a lipid acceptor in serum) spontaneously acquires lipids from these domains (Fig). Based on our biochemical and cell biological data, we propose "the direct loading model," a mechanism quite different from the conventional model.

【Research Methods】

To provide answers to unsolved questions in this field, we will integrate a variety of scientific and technical disciplines, including single molecule imaging, cryo-electron microscopy, high-speed AFM, high-resolution X-ray crystallography, and studies in model organisms in addition to conventional biochemistry and cell biology.



Models of HDL formation

We recently reported that ABCA1 is involved in the uneven distribution of cholesterol in the plasma membrane. Our ongoing studies will reveal the mechanism by which ABCA1 function is regulated. Lipid-transporting ABC proteins are thought to be involved in neurological diseases such as Alzheimer's. Our studies will reveal their roles in these disorders using model organisms.

【Expected Research Achievements and Scientific Significance】

Collapse of cholesterol homeostasis causes various diseases. However, the mechanism by which this homeostasis is maintained remains unclear, and the physiological role of cholesterol is not well understood. By revealing the mechanism underlying HDL generation and novel physiological functions of cholesterols, our study will facilitate the development of methods to cure and prevent diseases such as atherosclerosis, diabetes, and neurological diseases.

【Publications Relevant to the Project】

・Nagata KO, *et al.* ABCA1 dimer-monomer interconversion during HDL generation revealed by single-molecule imaging. **Proc. Natl. Acad. Sci. USA**, 110, 5034-5039 (2013)
・Liu SL, *et al.* Orthogonal lipid sensors identify transbilayer asymmetry of plasma membrane cholesterol. **Nature Chem Biol** 13, 268-274 (2017)
・Ishigami M, *et al.* Temporary sequestration of cholesterol and phosphatidylcholine within extracellular domains of ABCA1 during nascent HDL generation. **Sci Rep.** 8:6170 (2018)

【Term of Project】 FY2018-2022

【Budget Allocation】 148,900 Thousand Yen

【Homepage Address and Other Contact Information】

http:// www.biochemistry.kais.kyoto-u.ac.jp/
uedak@kais.kyoto-u.jp