【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project : Elucidation of the integrated cellular network for mitochondrial biogenesis

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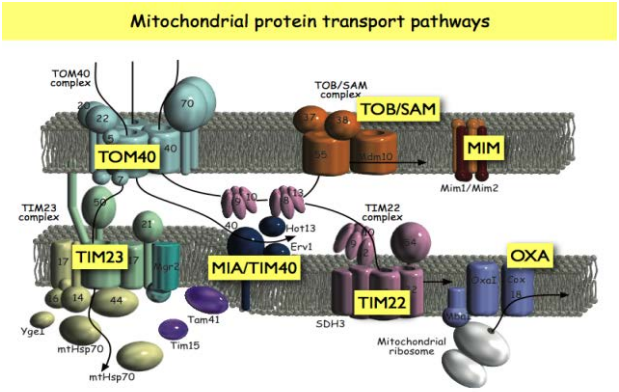
Research Project Number : 15H05705 Researcher Number : 70152014
Research Area : Structural Biochemistry
Keyword : Mitochondria, protein transport, lipid transport, organelle, biological membrane

【Purpose and Background of the Research】

Mitochondria are essential for the viability of all eukaryotic cells. They function as powerhouses for production of ATP, are crucial for the metabolism of amino acids, lipids and iron, and play a central role in apoptosis. Defects in mitochondrial biogenesis and functions lead to severe diseases in particular of the nervous system, heart and muscles. Since mitochondria are only generated by growth and division of preexisting mitochondria or require them as templates, mitochondrial growth relies on precise import of their resident proteins, thus protein import constituting the central process of mitochondrial biogenesis.



Pathways for mitochondrial protein trafficking

【Research Methods】

In this project, we make full use of technologies in biochemistry, cell biology, molecular genetics, and structural biology to resolve the following questions. (P1) How are the gates of the translocator channels open to release membrane proteins laterally? (P2) How can the lateral release of PINK1 be controlled by proteinaceous factors and chemical substances? (P3) What are the mechanisms of quality control for non-stop mitochondrial proteins? (L1) How to establish reliable lipid transport assays *in vitro*? (L2) What is the mechanism of lipid transport by ERMES, a tethering complex between the ER and mitochondria? (L3) What are the factors that physically tether the mitochondrial membrane with those in other organelles? (L4) What is the mechanism of lipid transport by Ups proteins? (L5) What is the significance of ERMES clustering and how is that controlled? (L6) How to develop a system to monitor lipid transport between distinct organelles *in vivo*?

【Expected Research Achievements and Scientific Significance】

The expected results of this project will radically change the view on organelle structures and functions; organelles are not distinct membrane surrounded structures that separate biochemical reactions from each other, but are bound to conduct coordinated performances through exchange of metabolites and information. Mitochondrial biogenesis will be thus understood by new viewpoint that integrates the dynamic mitochondrial protein trafficking network into a sophisticated cellular regulatory systems of mitochondrial bioenergetics, structure organization, phospholipid biosynthesis and transport. Since mitochondria play central functions in the cells and are involved in the pathogenesis of numerous diseases, the obtained results will be giving significant impact on the understanding of cellular functions in health and disease and connect different fields from basic biology to molecular medicine as well.

【Publications Relevant to the Project】

Y. Watanabe *et al.* (2015) Structural and mechanistic insights into phospholipid transfer by Ups1–Mdm35 in mitochondria. *Nat. Commun.* in press.

J. Song *et al.* (2014) A novel import route for an N-anchor mitochondrial outer membrane protein aided by the TIM23 complex. *EMBO Rep.* 15, 670-677.

【Term of Project】 FY2015-2019

【Budget Allocation】 349, 300 Thousand Yen

【Homepage Address and Other Contact Information】 http://endolab.jp/wp/