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Intracellular lipid trafficking and organelle biogenesis

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Research impact at a glance

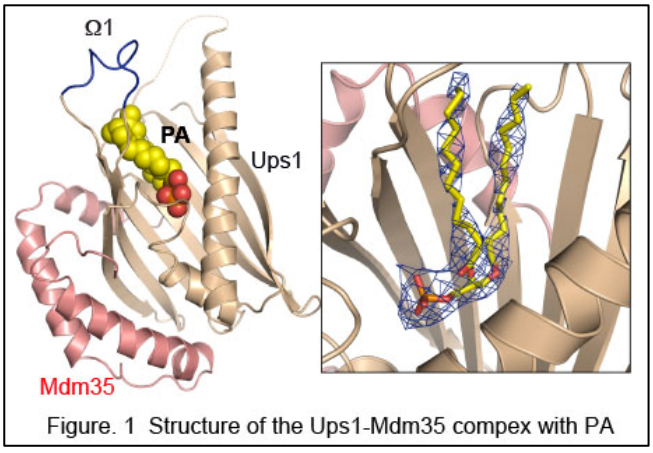

Figure. 1 Structure of the Ups1-Mdm35 compex with PA

1. Cardiolipin (CL), the mitochondrial signature phospholipid, is synthesized from a high-energy intermediate phospholipid, CDP-diacylglycerol. We identified a novel mitochondrial enzyme named Tam41 that mediates conversion of phosphatidic acid (PA) to CDP-diacylglycerol in mitochondria, filling in the last piece of the puzzling CL synthesis[1].

2. For CL synthesis, PA has to be transported from the mitochondrial outer to inner membrane. We demonstrated that the PA transfer is directly mediated by the Ups1-Mdm35 complex, which is the first lipid transfer machinery found in mitochondria[2].

3. We succeeded in developing a novel *in vitro* assay system to directly analyze phospholipid transport between the endoplasmic reticulum (ER) and mitochondria. Using this system, we settled a dispute over the phospholipid transfer function of the ERMES (ER-Mitochondria Encounter Structure) complex, which is responsible for physical tethering between the ER and mitochondria[3].

Detailed description of the research

Background: In eukaryotic cells, complex membrane structures called organelle are developed to carry out their characteristic functions. Maintaining appropriate phospholipid compositions of the membranes is essential for functional integrity of the organelles. Since cellular locations for phospholipid synthesis are limited to the ER membrane and the mitochondrial inner membrane, newly synthesized phospholipids have to be distributed properly from the ER or mitochondria to other cellular membranes. We are very much interested in understanding of molecular mechanisms of intracellular phospholipid transport, which is an important open question in cell biology.

On-going research: 1. Intracellular Phospholipid Transport and Organellar Mass in a Cell

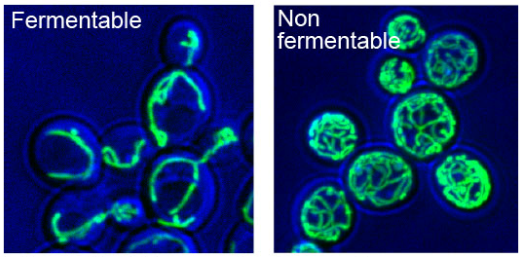

Figure.2 Mitochondria in yeast cells

Mitochondria are highly dynamic organelles with diverse functions and dynamically alter their morphology to adapt cellular demand. Figure 2 shows yeast mitochondria when cultured under a fermentable or a nonfermentation condition in which mitochondrial respiration is essential for growth. Interestingly, mitochondrial volume is dramatically increased upon shifting to the nonfermentable condtion. In order to understand such dynamic feature of mitochondria, we have been elucidating molecular mechanisms of intracellular phospholipid traffic.

2. Organelle-Organelle Tethering

Recent studies have shown that distinct organelles physically connect and communicate with each other to maintain the integrity of their functions.

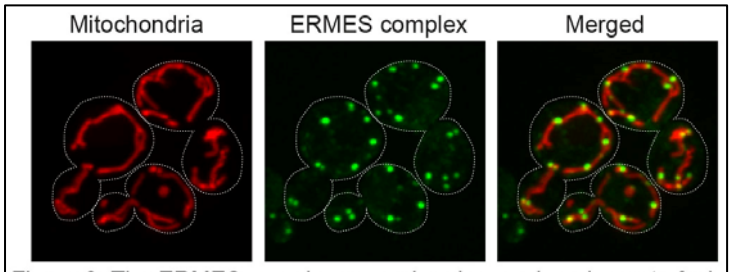

Figure 3. The ERMES complexes can be observed as descrete foci.

In yeast, multiple inter- and intra-mitochondrial membrane contact sites were identified to date and were proposed to be involved in phospholipid biogenesis[4]. Although it is clear that the ERMES complex tethers the ER and the mitochondrial outer membrane, it is still largely unknown whether other organelles also form such organelle contact sites. We thus developed an assay system to observe organelle-organelle interactions under a fluorescent microscope and are now searching yet-to-be identified organelle tethering proteins.

Selected publications

1. Tamura Y. Harada Y. Nishikawa S. Yamano K. Kamiya M. Shiota T. Kuroda T. Kuge O. Sesaki H. Imai K. Tomii K. and Endo T.* (2013) Tam41 is a CDP-diacylglycerol synthase required for cardiolipin biosynthesis in mitochondria. ***Cell Metab.***, 17, 709-718.

2. Watanabe Y. Tamura Y. Kawano S. and Endo T*. (2015) Structural and mechanistic insights into phospholipid transfer by Ups1–Mdm35 in mitochondria. ***Nat. Commun.*** 6, Article number: 7922.

3. Kojima R. Endo T. and Tamura Y. (2016) A phospholipid transfer function of ER-mitochondria encounter structure revealed in vitro. ***Sci. Rep.*** 6, Article number: 30777.

4. Tamura Y. and Endo T. (2017) Role of intra- and inter-mitochondrial membrane contact sites in yeast phospholipid biogenesis. *Advances in Experimental Medicine and Biology*, (ed. Mitsuo Tagaya and Thomas Simmen), Springer. *in press*.