学位論文抄録

Two Cdc48 cofactors Ubp3 and Ubx2 regulate mitochondrial morphology and protein turnover
（Cdc48 の 2 つの補因子 Ubp3 と Ubx2 はミトコンドリアの形態とタンパク質分解を制御する）

チョードリー　アビジット

Chowdhury　Abhijit

熊本大学大学院医学教育部博士課程医学専攻
HIGOプログラム4年コース

指導教員

小椋　光　教授
熊本大学大学院医学教育部博士課程医学専攻分子細胞制御学

Abstract of the Thesis

Background and purpose: Mitochondria are dynamic organelles constantly undergoing coordinated fusion and fission during vegetative growth to maintain their homogeneity. We have shown that a cytosolic AAA ATPase, Cdc48, is involved in the regulation of mitochondrial fusion and turnover of a fusion-responsible GTPase, Fzo1, in the mitochondrial outer membrane. Two distinct poly-ubiquitylations of Fzo1 are required for the mitochondrial fusion and the Fzo1 turnover, respectively, and these poly-ubiquitin chains are removed by two deubiquitylation enzymes, Ubp2 and Ubp12, respectively. Thus, it was assumed that multilayer ubiquitylation cascades regulate Fzo1. In this study, we explored cofactor proteins of Cdc48 regulating mitochondria morphology and Fzo1 turnover.

Methods: Mitochondria-targeting GFP was expressed in the budding yeast *Saccharomyces cerevisiae*, and mitochondrial morphology was analyzed by fluorescent microscopy. Protein turnover rates of HA-tagged Fzo1, Ubp2, and Ubp12 were analyzed by the cycloheximide-chase assay.

Results: We analyzed mitochondrial morphology and Fzo1 turnover rates in Cdc48 cofactor-deleted strains, and identified Ubp3 and Ubx2 as cofactors, which regulate mitochondria-relating Cdc48 functions. Lack of Ubp3 caused fragmented and aggregated mitochondria without affecting Fzo1 turnover. Ubp12 was stabilized in the *ubp3*-deletion strain. Thus, Ubp3 facilitates degradation of Ubp12, leading to accumulation of fusion-competent poly-ubiquitylation of Fzo1. In contrast, Fzo1 turnover was delayed in *ubx2*-deleted cells without alteration of mitochondrial morphology, and sucrose density gradient centrifugation revealed that the loss of Ubx2 affected Fzo1 oligomer disassembly. The cell lacking Ubx2 showed destabilization of Ubp2, indicating direct involvement of the Cdc48-Ubx2 complex in Fzo1 turnover.

Conclusion: Two Cdc48 cofactors Ubx2 and Upb3 independently regulate Fzo1, Ubp2, and Ubp12, thereby regulating mitochondrial fusion and protein turnover.