Special Lecture Tokuron

基盤医学特論

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Dr. Chao-Wen Wang（王昭雯）

Academia Sinica（中央研究院）
Taipei, Taiwan（台湾）

Seipin: A guardian of lipid metabolism?
セイピンは脂肪代謝の守護神か？

A growing list of proteins and enzymes are involved in maintaining a proper lipid droplet (LD) function. Some LD surface proteins are enzymes involved in lipid metabolism, as they synthesize neutral lipids and phospholipids, and liberate stored lipids. Several other proteins are required for LD formation, maintenance or growth, i.e. to convert nascent to mature LDs. Probably the most prominent member of proteins associated with LD biology is seipin, a homo-oligomeric integral membrane protein which appears to concentrate and act at contact sites between nascent LDs and the endoplasmic reticulum (ER) to promote LD maturation, but its exact molecular function remains obscure.

The main feature of seipin-deficient cells is the formation of irregularly shaped, small clustered and aggregated, or ‘‘supersized’’ LDs, and patients with loss-of-function mutations in seipin suffer from congenital generalized lipodystrophy (CGL), an autosomal recessive disorder characterized by a near-total loss of adipose tissue, severe insulin resistance, hypertriglyceridemia, and fatty liver. While the function of seipin is not clear, seipin gene manipulation in yeast, worms (our unpublished results), flies, mice, and human cells indicate structural as well as regulatory roles LD biogenesis and maintenance and lipid metabolism. This raises the interesting question whether these observations can be assigned to one central role of seipin in lipid homeostasis, or whether there is more than one distinct function of seipin?

We have shown previously that yeast seipin is a complex of Sei1 and Ldb16. Taken advantage of a large-scale protein purification experiment, we have identified various lipid metabolic enzymes, including sphingolipid biosynthesis enzymes, as putative seipin interacting partners. We noticed that yeast seipin mutants indeed showed altered sphingolipid regulatory phenotypes that can be complemented by expressing human seipin. Lipidomic analyses revealed that the seipin mutants accumulated more sphingoid precursors, including long chain bases and ceramides, which can be explained by higher serine palmitoyltransferase (SPT) and fatty acid elongase activities observed in the mutant strains. Seipin interacts with the SPT and elongase complexes through Sei1 and the first cytoplasmic domain of Sei1 plays an important role for mediating the interaction. Intriguingly, the degrees of seipin-SPT and seipin-elongase interactions are sensitive to the level of sphingolipids, implying a feedback control by which the cell maintains sphingolipid homeostasis through regulating these interactions. In addition, we discovered that seipin interacts with the SPT and elongase enzymes at a discrete subdomain of the ER, supporting a locally regulated sphingolipid production. Taken together, our findings raise the interesting hypothesis that lipid metabolic enzymes might get concentrated and controlled at specific membrane subdomains, such as LD-ER-vacuole contact sites, mediated by seipin oligomer platforms.

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