Identification and Functional Analysis of Lipid Droplet Autophagy Receptors From 48 Candidates

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How do cells decide which lipid droplets to eliminate? Cells store excess lipids in lipid droplets (LDs) to maintain energy balance and protect themselves from lipotoxicity. However, when lipid storage becomes excessive or when cells need energy, LDs must be selectively degraded to maintain cellular homeostasis. Failure to properly regulate LD degradation has been linked to multiple diseases, including nonalcoholic fatty liver disease, Alzheimer's disease, and Parkinson's disease. Lipophagy, a selective form of autophagy, mediates the delivery of LDs to lysosomes or vacuoles for degradation. Despite its importance, the molecular mechanisms that determine which LDs are targeted for lipophagy remain poorly understood. In this study, we screened 48 LD-associated membrane protein deletion strains in Saccharomyces cerevisiae. Eight deletions-17% of candidates-consistently impaired LD clearance, defining the membrane determinants required for lipophagy. Among these, Pln1 showed the strongest reduction in lipophagy, suggesting it functions as a putative selective lipophagy receptor. Its human counterparts, the Perilipins, are established regulators of lipid metabolism and are implicated in fatty liver disease. Our results suggest that specific LD membrane proteins play critical roles in mediating selective lipophagy. These findings provide new insights into how cells regulate lipid storage and degradation, offering a framework for understanding lipid metabolism and its relevance to metabolic and neurodegenerative disease.

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