Seipin mediates sphingolipid homeostasis at a subdomain of the endoplasmic reticulum in close vicinity to the lipid droplet

Chao-Wen Wang*, Yi-Hsiu Lin, Wei-Cheng Su, Martin Pagac

Institute of Plant and Microbial Biology, Academia Sinica, Nankang, Taipei, 11529, TAIWAN

* **Corresponding author:** cwwang02@gate.sinica.edu.tw

Seipin is known for its critical role in controlling lipid droplet (LD) assembly at the LD-forming subdomain of the endoplasmic reticulum (ER). Here, we identified seipin as a homeostatic regulator for sphingolipid synthesis. Yeast cells lacking seipin showed altered sensitivity to sphingolipid inhibitors, accumulated sphingoid intermediates, and increased serine palmitoyltransferase (SPT) and fatty acid (FA) elongase activities. Seipin negatively regulated sphingolipid synthesis by binding with the SPT and FA elongase enzymes, which was reduced in a concentration-dependent manner when sphingolipid synthesis was hampered by inhibitor treatment. The inhibitory interactions of seipin with SPT and FA elongase co-localized at ER-LD contacts, although were likely regulated differentially. We found that LD biogenesis was normal when SPT activity was blocked, but excess sphingoid intermediates may affect LD morphology. Given that human seipin expression rescued the altered sphingolipids in yeast seipin mutants, the sphingolipid homeostastic control mechanisms involving seipin may be a conserved feature through evolution.