UC San Diego

UC San Diego Previously Published Works

Title

Receptor—cargo coupling during ER-autophagy depends on coat proteins and ER membrane properties

Permalink

https://escholarship.org/uc/item/79b4b2f8

Journal

Autophagy, ahead-of-print(ahead-of-print)

ISSN

1554-8627

Authors

Chen, Shuliang

Banerjee, Subhrajit

Novick, Peter

et al.

Publication Date

2026-07-03

DOI

10.1080/15548627.2026.2695313

Copyright Information

This work is made available under the terms of a Creative Commons Attribution-NoDerivatives License, available at https://creativecommons.org/licenses/by-nd/4.0/

Peer reviewed

eScholarship.org Powered by the California Digital Library
University of California

Autophagy

Autophagy

ISSN: 1554-8627 (Print) 1554-8635 (Online) Journal homepage: www.tandfonline.com/journals/kaup20

Receptor–cargo coupling during ER-autophagy depends on coat proteins and ER membrane properties

Shuliang Chen , Subhrajit Banerjee , Peter Novick , William A. Prinz & Susan Ferro-Novick

To cite this article: Shuliang Chen , Subhrajit Banerjee , Peter Novick , William A. Prinz & Susan Ferro-Novick (03 Jul 2026): Receptor–cargo coupling during ER-autophagy depends on coat proteins and ER membrane properties, Autophagy, DOI: 10.1080/15548627.2026.2695313

To link to this article: https://doi.org/10.1080/15548627.2026.2695313

© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.

Published online: 03 Jul 2026.

Submit your article to this journal

Article views: 663

View related articles

View Crossmark data

Full Terms & Conditions of access and use can be found at
https://www.tandfonline.com/action/journalInformation?journalCode=kaup20

AUTOPHAGY
https://doi.org/10.1080/15548627.2026.2695313

Taylor & Francis
by informa

AUTOPHAGIC PUNCTUM

OPEN ACCESS Check for updates

Receptor–cargo coupling during ER-autophagy depends on coat proteins and ER membrane properties

Shuliang Chen[a], Subhrajit Banerjee[b], Peter Novick[a], William A. Prinz[b], and Susan Ferro-Novick[a]

[a]Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla CA, USA; [b]Department of Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX, USA

ABSTRACT

Selective autophagy of the endoplasmic reticulum (reticulophagy) is driven by receptor-mediated ER remodeling. Reticulophagy receptors are essential for ER turnover. Productive cargo recognition during autophagosome-mediated reticulophagy depends on the interaction of the receptor with the COPII subunit Sfb3/Lst1 (SEC24C in mammals) as well as the phospholipid composition of the ER. We unexpectedly found that the conserved reticulophagy receptor Atg40 traffics to the vacuole/lysosome without cargo (ER membrane proteins) or Sfb3/Lst1 in neutral lipid-deficient mutant cells. Comprehensive lipidomic profiling of this lipid mutant revealed a shift in the phosphatidylethanolamine (PE)-to-phosphatidylcholine (PC) ratio, a compositional change predicted to alter biophysical properties of the ER, including membrane bendability. The discovery that membrane properties regulate receptor – cargo coupling efficiency at autophagic sites, as they do at secretory exit sites, extends current mechanistic models of reticulophagy and suggests membrane properties may also affect cargo selection on other types of selective autophagy pathways.

ARTICLE HISTORY
Received 22 June 2026
Accepted 23 June 2026

KEYWORDS
Coat proteins; membrane curvature; neutral lipid; receptor–cargo coupling; reticulophagy

Reticulophagy is a selective autophagy pathway that maintains homeostasis during cell stress by selectively degrading ER domains that are superfluous, damaged, or contain misfolded proteins. Although ER-associated degradation (ERAD) clears most misfolded proteins, aggregation-prone or ERAD-resistant substrates must be eliminated via reticulophagy. During reticulophagy, ER subdomains are selectively sequestered into sealed double-membrane structures called autophagosomes that are subsequently delivered to the vacuole (in yeast) or lysosome (in mammals) for degradation. This selectivity relies on autophagy receptors that bind lipidated Atg8 (LC3 in mammals) to couple ER fragments to the core autophagy machinery. The receptor connects cargo to the autophagy machinery by binding to Atg8 via its AIM (**A**tg8 **I**nteracting **M**otif). In the yeast *Saccharomyces cerevisiae*, ER autophagy is mediated by the conserved reticulophagy receptor, Atg40. The reticulon homology domain (RHD) in Atg40 enriches it in ER tubules and the highly curved edges of sheets, regions where reticulophagy typically occurs.

Genetic and biochemical studies in yeast identified the COPII coat subunit Sfb3/Lst1 (SEC24C in mammalian cells) as a critical binding partner of Atg40. Sfb3/Lst1 forms a stable complex with Sec23 and functions as a dual-purpose player, acting in both ER-Golgi traffic and reticulophagy. When reticulophagy is induced by conditions such as rapamycin treatment, Atg40 actively recruits the Sfb3/Lst1-Sec23 complex from the cytosol to autophagic sites on the ER. Although the precise role of Sfb3/Lst1 at these sites has been unclear, our recent studies have revealed an essential function in reticulophagy that is distinct from its canonical role in secretion [1].

In this study, we asked whether the lipid composition of the ER affects cargo-capture during reticulophagy. This is a difficult question to address as most ER lipid changes that affect reticulophagy also disrupt autophagosome formation, making it challenging to assess reticulophagy-specific effects. We were able to overcome this challenge by using a lipid mutant that disrupts rapamycin-induced reticulophagy, but not bulk autophagy. This mutant lacks the four proteins that produce triglycerides and steryl esters, the neutral lipids that are stored in lipid droplets (LDs), consequently these cells lack LDs. The use of this lipid mutant (ΔLD) provided us with a unique opportunity to directly assess how ER lipid composition regulates cargo capture during reticulophagy. Strikingly, in neutral lipid – deficient cells or in cells lacking Sfb3/Lst1, we found that Atg40 trafficked to the vacuole without cargo proteins (Rtn1, Sec66, Sec63, Sec61, Per33), which remained in the ER. The uncoupling of Atg40 from its cargo, in cells lacking Sfb3/Lst1 or neutral lipids, revealed a requirement for coat proteins and ER phospholipids in receptor-cargo coupling.

Analysis of the ER lipid composition of cells lacking LDs revealed an altered ratio of PE:PC. This shift in phospholipid composition is known to have important biophysical consequences. PE is a conical lipid, while PC is cylindrical. The different chemical properties and shapes of PE and PC in membranes are thought to change the biophysical properties of a membrane, including bendability, fluidity, and packing.

CONTACT Susan Ferro-Novick sferronovick@health.ucsd.edu Department of Cellular and Molecular Medicine, University of California at San Diego, La Jolla, CA 92093

© 2026 The Author(s). Published by Informa UK Limited, trading as Taylor & Francis Group.
This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial-NoDerivatives License (http://creativecommons.org/licenses/by-nc-nd/4.0/), which permits non-commercial re-use, distribution, and reproduction in any medium, provided the original work is properly cited, and is not altered, transformed, or built upon in any way. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

During the formation of ER-Golgi transport carriers, COPII coat machinery coordinates cargo selection and membrane bending to generate coated vesicles that bud from ER exit sites (ERES). Similarly, during reticulophagy cargo is sequestered at specialized sites in the ER called ER autophagy sites (ERPHS) that are distinct from ERES. Cargo sequestration during autophagosome-mediated reticulophagy uses only Sfb3/Lst1/SEC24C-SEC23 and not the full complement of COPII coat subunits used on the secretory pathway. We propose that ER transmembrane cargoes that undergo reticulophagy enter ERPHS from negatively curved ER domains (Figure 1). In neutral lipid – deficient cells (ΔLD), the reduced PE:PC ratio is predicted to decrease ER membrane bendability and negative curvature, impairing the recruitment of Lst1-Sec23 and cargo into ERPHS. Atg40 still enters the ERPHS in the ΔLD cells via a direct interaction with Atg8, but Sfb3/Lst1-Sec23 and its associated cargo accumulate next to the ERPHS and consequently are excluded from autophagosomes (Figure 1).

Membrane curvature also appears to play an important role in mammalian reticulophagy. We previously showed that SEC24C associates with the reticulophagy receptor RTN3L at peripheral ER junctions, ER subdomains with high negative curvature. Just as Sfb3/Lst1-Sec23 is recruited to negatively curved membranes at ERPHS in yeast, SEC24C-SEC23 is enriched at tubule junctions that contain high negative curvature. Misfolded ERAD-resistant proteins are targeted for degradation by RTN3L-SEC24C-mediated reticulophagy at autophagic sites that form at tubule junctions. Our studies suggest that negative curvature, which is affected by ER lipid composition, is a regulator of reticulophagy. We propose that the lipid composition of the ER and the geometry of ER tubules influence the spatial recruitment of selective autophagy machinery and the packaging of resident ER cargoes into autophagosomes. In the future it will be important to address whether other autophagy receptors function with SEC24C-SEC23 during reticulophagy. Addressing how reticulophagy receptors interact with SEC24C-SEC23 to form autophagic sites and capture cargo into ERPHS has important implications for understanding how mammalian receptors function.

When reticulophagy is induced, Atg40 binds to Atg8 and recruits the Sfb3/Lst1-Sec23 complex to negatively curved membranes. This leads to the enrichment of cargo proteins (Rtn1 and Sec66) into autophagic sites (ERPHS). In ΔLD cells, the lower PE:PC ratio of the ER membrane reduces its bendability and fluidity, effectively uncoupling the coat and cargo from the receptor. Atg40 retains access to the ERPHS via its ability to bind to Atg8, but it can no longer sequester cargo or coat proteins into these sites. Consequently,

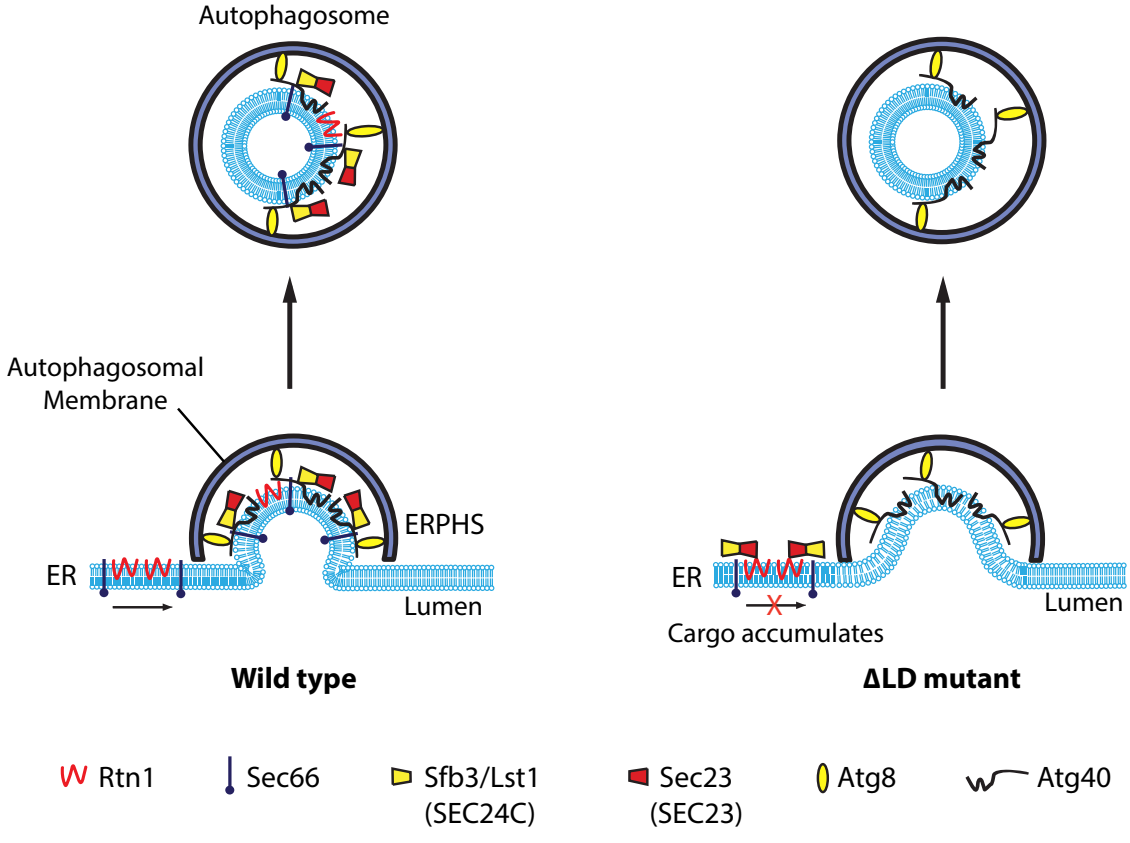

Figure 1. Cargo fails to be coupled to the autophagy receptor in ΔLD cells.

autophagosomes that traffic to the vacuole contain Atg40, but not cargo or Sfb3/Lst1-Sec23. The mammalian homologs of Sfb3/Lst1-Sec23 are indicated in brackets.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Author contributions

CRediT: **Shuliang Chen:** Writing – original draft, Writing – review & editing; **Subhrajit Banerjee:** Writing – review & editing; **Peter Novick:** Funding acquisition, Writing – review & editing; **William A. Prinz:** Funding acquisition, Writing – review & editing; **Susan Ferro-Novick:** Funding acquisition, Writing – review & editing.

Funding

SC and SF-N received salary support from NIGMS under [grant R35GM131681]. PN received salary support from NIGMS under [grant R01GM35370]. SB and WAP were supported by [R35GM153315].

Data availability statement

This study does not present new primary data. The original findings can be found in the referenced publication.

Reference

[1] Chen S, Banerjee S, Liu D, et al. Coupling of cargo to the autophagy receptor is a critical step in ER-phagy. Sci Adv. 2026;12(24):eaee9856. doi: 10.1126/sciadv.aee9856