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Point

TECPR1-Mediated Tubulation Drives Lysosomal Membrane Repair Independent of Canonical Autophagy and CASM

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Abstract: Lysosomal membrane integrity is essential for cellular homeostasis, yet how lysosomes are repaired during metabolic stress remains incompletely understood. In our recent study, we found that lysosomal uptake of lipid droplets during glucose starvation induced lysosomal membrane damage and identified TECPR1 as a key mediator of lysosomal membrane repair. TECPR1 was recruited to compromised lysosomes by binding PI4P on damaged membranes and subsequently engaged KIF1A to drive lysosome-derived membrane tubulation. This tubulation facilitated the removal of damaged membrane components and promoted lysosomal recovery. Functionally, TECPR1-dependent repair maintained lipid metabolic homeostasis and supported cell survival under energy stress. *In vivo*, TECPR1 deficiency aggravated starvation-induced liver injury in a high-fat diet-induced MAFLD model. In this U&A Point, we discuss this TECPR1-mediated, tubulation-based lysosomal repair pathway and its mechanistic distinction from canonical autophagy and CASM.

Keywords: Autophagy; CASM; TECPR1; Tubulation; Lysosomal membrane repair

Lysosomes play a central role in cellular homeostasis by supporting degradative and recycling processes, yet the mechanisms that preserve lysosomal membrane integrity during energy stress remain incompletely understood. In our recent study [1], we found that lipid droplet uptake by lysosomes during glucose starvation was able to induce lysosomal membrane damage. We identified TECPR1 as a key factor required for lysosomal membrane repair under conditions of glucose deprivation or LLOMe-induced lysosomal membrane permeabilization. TECPR1 was recruited to damaged lysosomes through its interaction with PI4P on compromised lysosomal membranes. Upon recruitment, TECPR1 associated with the kinesin motor protein KIF1A to promote membrane tubulation from damaged lysosomes, thereby facilitating the removal of damaged membrane components and enabling lysosomal repair. Functionally, TECPR1-dependent lysosomal repair was required to maintain lipid metabolic homeostasis and promote cell survival during energy stress. Furthermore, loss of TECPR1 exacerbated starvation-induced liver injury in a high-fat diet–induced MAFLD mouse model. Our study revealed a new function of TECPR1 in lysosomal repair (Figure 1).

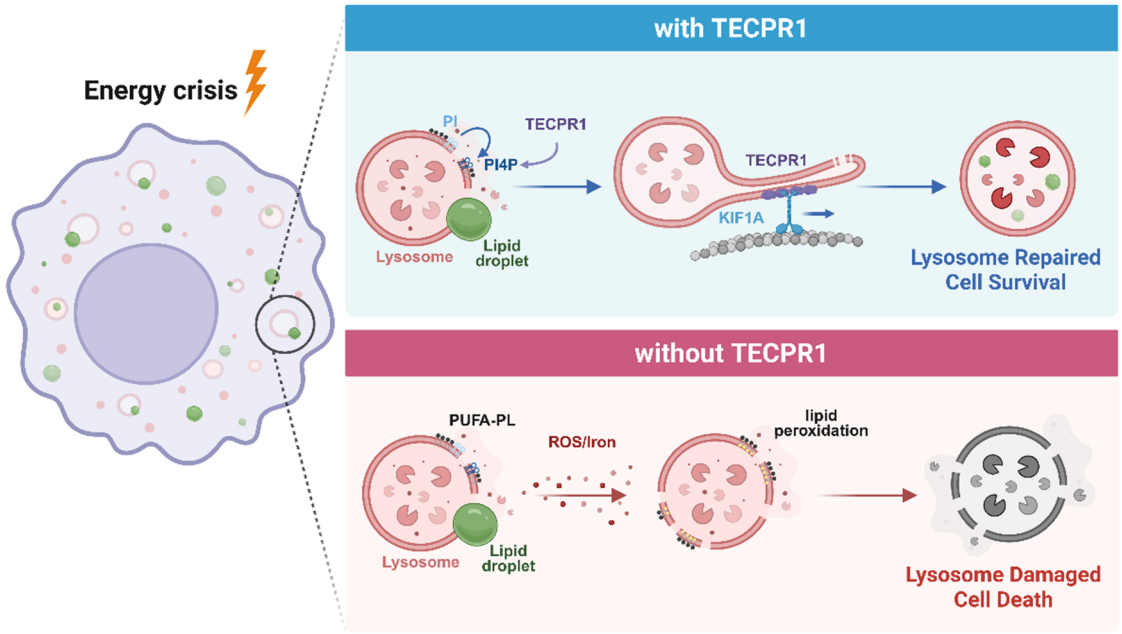

Figure 1. TECPR1-mediated lysosomal membrane repair during energy stress.

TECPR1 contains two WD-40–like TECPR domains, two dysferlin domains, an AIR, and a PH domain, suggesting its capacity to coordinate protein–protein and protein–lipid interactions. Previous work from our laboratory identified TECPR1 as a regulator of canonical autophagy. Through its AIR domain, TECPR1 directly associated with the ATG12–ATG5 conjugate, while its PH domain bound PI3P in an ATG12–ATG5-dependent manner. By simultaneously engaging the ATG12–ATG5 conjugate and PI3P, TECPR1 promoted autophagosome–lysosome fusion. In parallel, studies from the Chihiro Sasakawa laboratory characterized TECPR1 as an ATG5-interacting protein required for selective autophagy of invading bacteria. In this context, TECPR1 bound WIPI2, a PI3P-binding protein on phagophores, and ATG5 on selective autophagy cargo, thereby bridging cargo to the autophagic membrane. Later, a 2020 study by Thomas Wollert's group proposed that TECPR1 bound LC3C through its N-terminal WD-40–like TECPR domain and bound to PI4P on lysosomes through its PH domain to promote autophagosome recruitment to lysosomes and enhance the degradation of disease-related protein aggregates in neural stem cells. Collectively, these studies establish TECPR1 as a tethering factor in autophagy that links selective autophagy cargo or lysosomes to autophagosomes.

More recently, three independent studies reported that TECPR1 was recruited to damaged lysosomes induced by LLOMe, GPN, or pathogen invasion and promoted CASM (conjugation of ATG8s to single membranes), a process that lipidates ATG8 proteins on the limiting membrane of single-membrane organelles, including lysosomes, to support membrane remodeling. In these contexts, TECPR1 bound sphingomyelin on damaged lysosomes via its dysferlin domain and subsequently functioned together with ATG5 and ATG12 to promote ATG8 lipidation on damaged lysosomal membranes. Another study by Wang et al. [2] further suggested that TECPR1 may be recruited to swollen lysosomes that exposed sphingomyelin, whereas TECPR1-dependent LC3 conjugation occurs preferentially on ruptured lysosomal remnants. TECPR1-dependent CASM may engage downstream noncanonical autophagy-related processes or lysosome recovery, through less-defined molecular mechanisms.

Our recent study demonstrated a CASM-independent direct role of TECPR1 in lysosome damaged membrane repair. In this process, TECPR1 was recruited to damaged lysosomes via binding to PI4P through its dysferlin domain and subsequently formed tubular structures through its interaction with motor protein KIF1A to remove damaged lysosomal membrane components. Importantly, TECPR1 recruitment and tubule formation were independent of canonical autophagy and CASM. We found that depletion of ATG5 or ATG16L1, two core components of CASM, caused only modest defects in lysosomal repair, whereas TECPR1 depletion resulted in a much more pronounced impairment. Furthermore, combined knockdown of ATG5, ATG16L1, and TECPR1 did not exacerbate the repair defect beyond that observed upon TECPR1 knockdown alone. These results indicate that TECPR1 has a distinct lysosomal repair function beyond its function in CASM.

It's worth noting that TECPR1 exhibits context-dependent lipid engagement in two respects. First, a single domain can interact with distinct lipids: in our *in vitro* co-flotation assays, the dysferlin domain binds PI4P and also interacts with sphingomyelin (SM). Consistent with this, under glucose starvation–induced lysosomal damage, PI4P depletion markedly suppresses TECPR1 recruitment to damaged lysosomes, whereas under

lysosomal damage induced by LLOMe, GPN, or pathogen invasion, SM depletion strongly inhibits TECPR1 recruitment. Second, distinct TECPR1 domains may contribute to the recognition of the same lipid depending on cellular context. Previous studies and our current work suggest that TECPR1 can engage PI4P through different domains across conditions, with the PH domain implicated in earlier autophagy-related settings and the dysferlin domain mediating recruitment to damaged lysosomes in our repair model. The structural determinants and regulatory logic underlying this context dependence remain to be defined.

While we have established a direct role for TECPR1 in lysosomal repair, its functional relationship with the ESCRT machinery remains unclear. Reciprocal depletion and time-course analyses showed that TECPR1 and ESCRT components were recruited independently and with comparable kinetics. Functional assays revealed that depletion of either TECPR1 or ESCRT (TSG101/ALIX) significantly impaired lysosomal repair. In a recent study by Corkery et al. [3], published shortly after our work, the authors proposed that ATG12–ATG5-ATG16L1/TECPR1-mediated CASM was required for ESCRT-mediated lysosome repair, elegantly illustrating the possible interplay between these two repair pathways.

Future studies will focus on elucidating lysosomal membrane repair mechanisms across a broader range of physiological and pathological contexts, including neurodegenerative diseases, cancer, aging, and drug-induced toxicity, as distinct modes of lysosomal damage may engage different repair pathways.

Taken together, our study defines a previously unrecognized role for TECPR1 in lysosomal quality control under metabolic stress. TECPR1 forms tubular structures at damaged lysosomes to remove damaged membrane components, representing a repair mechanism that is distinct from its previously described functions in canonical autophagy and CASM.

During glucose starvation, lysosomal uptake of lipid droplets induces lysosomal membrane damage. TECPR1 is recruited to damaged lysosomes via interaction with PI4P on compromised membranes. Once recruited, TECPR1 engages the kinesin motor KIF1A to drive membrane tubulation from damaged lysosomes, facilitating the removal of damaged membrane components and promoting lysosomal repair. This repair mechanism is essential for maintaining lipid metabolic homeostasis and supporting cell survival under energy stress. *In vivo*, TECPR1 deficiency exacerbates starvation-induced liver injury in a high-fat diet–induced MAFLD mouse model.

Author Contributions

Q.Z., X.L. and H.C. conceived the idea of the review. H.C., C.Z. and X.L. conducted the literature search and analysis. X.L. and H.C. wrote the first draft of the manuscript. X.L. and Q.Z. critically revised the manuscript. All authors reviewed and approved the final version of the manuscript.

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Institutional Review Board Statement

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Informed Consent Statement

Not applicable.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

No AI tools were utilized for this paper.

Abbreviations

AIR	ATG12-interacting region
ATG	autophagy-related gene
CASM	conjugation of ATG8 to single membranes
ESCRT	endosomal sorting complexes required for transport
GPN	glycyl-L-phenylalanine 2-naphthylamide
KIF1A	kinesin family member 1A
LC3	microtubule-associated protein 1 light chain 3
LLOMe	L-leucyl-L-leucine methyl ester
MAFLD	metabolic-associated fatty liver disease
PH	pleckstrin homology
PI4P	phosphatidylinositol 4-phosphate
PI3P	phosphatidylinositol 3-phosphate
TECPR1	tectonin beta-propeller repeat containing 1
WD-40	tryptophan–aspartic acid repeat domain
WIPI2	WD repeat domain phosphoinositide-interacting protein 2
PUFA-PL	polyunsaturated fatty acid–containing phospholipids
ROS	reactive oxygen species

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