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Nucleophagy: A two-step exit with the help of an outsider

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Maintenance of nuclear surveillance and quality control is paramount to a cell's long-term survival and function. A new study reveals how nucleophagy achieves the selective recycling of nuclear components via the autophagic pathway in the cytoplasm without compromising the integrity of the nuclear envelope.

The fundamental role of the nucleus in the establishment and maintenance of eukaryotic cell identity cannot be overstated. Defects associated with the nucleus, such as aberrant nuclear architecture, nucleolar expansion, genome instability, DNA damage, and telomere attrition, have been linked with pronounced cellular dysfunction and severe pathology in humans, resulting in progeroid syndromes and other age-related disorders[1]. Thus, not surprisingly, cells possess and mobilize elaborate quality control systems to surveil the integrity of the genomic material, the fidelity of DNA replication and mRNA transcription, as well as the preservation of a functional proteome, required for these critical quality control processes[2]. To complement these defenses, nuclear macroautophagy (nucleophagy) emerges as a crucial mechanism that selectively targets nuclear components for degradation via the cytoplasmic autophagy–lysosome pathway under various physiological and pathological contexts[3]. In a recent study published in *Nature Cell Biology*, Mannino *et al.*[4] provide mechanistic insights into the process of extracting nuclear cargo from the nucleus, while at the same time safeguarding the integrity of the nuclear envelope.

The nuclear envelope constitutes a structural and functional specialization of the endoplasmic reticulum (ER). Notably, nuclei have no internal membranes to compartmentalize their multifaceted functions: they instead rely on the formation of microdomains by co-assembly of functional complexes. It is conceivable that isolation of specific membrane fractions of the nuclear envelope or the ER is orchestrated in order to facilitate the selective elimination of damaged nuclear or ER components.

Selective autophagy of particular cellular components involves selective autophagy receptors. In yeast, Atg39 was identified as such a receptor at the perinuclear ER and the nuclear envelope, where it physically links the outer nuclear membrane (ONM) to the inner nuclear membrane (INM) via its amino-terminal transmembrane domain and carboxy-terminal membrane-binding amphipathic helices[5]. While the function of Atg39 as a dedicated receptor for nucleophagy has been established, multiple important facets of the process have remained obscure. What is the precise choreography of the molecular and morphological events that transpire during Atg39-mediated nucleophagy? How are the nuclear envelope membranes remodeled to allow excision of nuclear cargo that subsequently becomes encapsulated into autophagosomes?

In a tour de force of sophisticated molecular genetic and temporal imaging analyses, combining lattice light-sheet microscopy, tomography, and correlative light and electron microscopy, Mannino *et al.*[4] shed new light on the kinetics and ultrastructural features of nucleophagy. The authors conducted a comprehensive and quantitative spatiotemporal dissection of nucleophagy dynamics in yeast cells, using advanced monitoring methodologies, to follow the individual steps and the timeline of nuclear cargo excision and subsequent autophagic recycling at the ultrastructural level. The first critical insight that emerged from this investigation settles the question of how nucleus-derived vesicles (NDVs) are generated during Atg39-dependent nucleophagy. It was hypothesized that these vesicles could form via a single evagination event, involving both the INM and ONM of the nuclear envelope. However, the observations of Mannino *et al.*[4] provide ample support for an alternative nucleophagic pathway by clearly establishing that this process involves two consecutive membrane fission steps: an initial INM fission, giving rise to an INM-derived vesicle (INMDV) in the perinuclear space, and a subsequent fission event at the ONM, which then releases a double-membraned vesicle to the cytosol (Figure 1).

Remarkably, Mannino *et al.*[4] found that ONM fission is carried out by the dynamin-like protein 1 (Dnm1), an ortholog of the DRP1 GTPase that is best known for driving mitochondrial fission[6]. Previous studies have implicated Dnm1 in two other types of selective autophagy — mitophagy and pexophagy[7,8] — but this is the first time that a DRP1 GTPase has been found to be involved in nuclear envelope remodeling events. Similar to mitophagy and pexophagy, the recruitment of Dnm1 at the ONM pinching site is mediated by Atg11, which is itself recruited by Atg39. The focal accumulation of Atg39 at distinct nuclear envelope sites has been suggested to couple the deformation of the ONM and INM, facilitating the initial steps of NDV formation[5]. In addition, Atg39 recruits the core autophagic machinery to the newly formed NDVs via interactions with the scaffold protein Atg11 and the ubiquitin-like protein Atg8. Loading of these double-membraned vesicles to autophagosomes is a characteristic of nuclear-envelope-derived cargo and also depends on the activity of Atg39.

Apart from the INM segments and associated components that are incorporated in the INMDVs themselves, it is not known whether these vesicles contain specific soluble content of nucleoplasmic origin. Nevertheless, autophagic recycling of nucleolar components, such as the nucleolar methyltransferase Nop1, is mainly mediated by Atg39-dependent nucleophagy. Indeed, previous work reported that deletion of the nucleus–vacuole junction protein Nvj1, which is required for piecemeal microautophagy of the nucleus, does not affect Nop1 degradation during rapamycin-induced autophagy[9]. Atg39-positive NDVs within autophagosomes have also been shown to contain nuclear components including the INM chromosome-linkage protein Src1, the ONM reductase Hmg1, and nuclear pore complexes[9–11].

It remains unclear whether INMDVs act as a vesicular platform, where damaged nuclear components are selectively sorted before being directed for autophagic degradation. INMDV formation could also serve as a mode of basal-level recycling of (possibly long-lived) nuclear envelope constituents. It is tempting to speculate that INMDVs may function as sensing probes, conveying perturbation of nuclear envelope homeostasis in the context of a surveillance and quality control mechanism. In mitochondria, a mechanism of constant import and degradation of the mitophagy-associated kinase PINK1 senses perturbations in mitochondrial homeostasis, such as mitochondrial import machinery clogging, mitochondrial membrane depolarization and protein misfolding[12,13]. These mitochondrial defects lead to stabilization of PINK1 at the OMN, facilitating the initiation of mitophagic degradation. By analogy, defective INMDV trafficking could trigger the nucleophagic degradation of vesicular cargo.

Notably, the findings of Mannino *et al.*[4] indicate that approximately one out of three INM fission events lead to ONM fission in a Dnm1-dependent manner. INMDVs escaping Dnm1-mediated fission events at the ONM are likely to be delivered to the ER lumen, where they may be subjected to ER-phagy-mediated degradation or serve other signaling functions. Pertinent to this potential role of INMDVs, an interesting follow-up question concerns the delineation of their proteome and lipidome. While technically challenging, this analysis could be facilitated by the quantitative monitoring and ultrastructural approaches developed by Mannino *et al.*[4].

Importantly, whether the role of DRP1 GTPases in ONM scission during nucleophagy is functionally conserved in mammals remains to be assessed. Further dissection of the processes by which nuclear constituents are selectively sequestered in autophagosomes for lysosomal degradation in mammalian cells may pave the way for the development of innovative approaches to treat diseases associated with the accumulation of mutant or misfolded proteins within the nucleus. Previous studies have identified an assortment of nuclear components captured by autophagosomal or autolysosomal structures in mammalian cells, including chromatin, histones, lamins, nesprin, DNA topoisomerase II A/B, fibrillarin, the deacetylase SIRT1 and nucleoporin 98[14–20]. At present, selective nucleophagy receptors have not been identified in mammalian cells. Our current understanding invites the hypothesis that at least one mechanism mediating nucleophagy selectivity in mammals involves the direct interaction of specific nuclear components (lamin B1, lamin A/C, nesprin and the deacetylase SIRT1) with LC3[16,18,20]. Whether such interactions are indeed necessary and/or sufficient to initiate selective nucleophagy remains to be elucidated.

Mannino *et al.*[4] have generated tools and resources that can be utilized to further advance our understanding of nucleophagy by addressing important remaining questions. Given the identification of Dnm1 as the effector responsible for ONM fission in the nucleophagic cascade, the question now arises of how the INM fission events generating the INMDV intermediates are accomplished: Dnm1 appears to be dispensable for this step. Another interesting question relates to the specific scope of selective autophagy (including nucleophagy) induction under conditions of nutrient deprivation. To induce Atg39-dependent nucleophagy, the authors impose nitrogen starvation conditions. It remains unclear whether, in nutrient scarcity, organelle-targeting autophagy serves a replenishing function, or a damage repair response, or both. Addressing these questions, and other opaque mechanistic aspects, will yield a

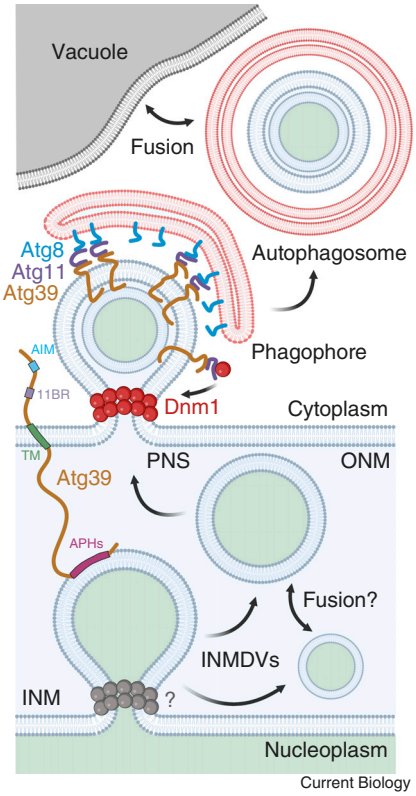

Figure 1. An unexpected role for the dynamin-like GTPase Dnm1 in nuclear envelope fission during Atg39-mediated nucleophagy in yeast.
Nucleophagy commences with focal accumulation of the selective autophagy receptor Atg39 at the nuclear envelope. Atg39 is a single-pass integral outer nuclear membrane (ONM) protein that physically couples the ONM to the inner nuclear membrane (INM) through its carboxy-terminal amphipathic helices (APHs), which engage the lumenal leaflet of the INM. Atg39 contains one Atg8-interacting motif (AIM) and one Atg11-binding region (11BR), located at its cytoplasmic amino terminus. Evagination and fission of the INM, via an unknown mechanism (indicated by ?), generates an INM-derived vesicle (INMDV) intermediate, which is released into the perinuclear space (PNS). Newly generated INMDVs may grow by fusion to form larger INMDVs. Atg11 recruits Dnm1 at the Atg39-positive sites of the NE to facilitate the sequestration and subsequent excision of the INMDVs through a second fission step of the ONM. The engagement of nuclear-derived vesicles (NDVs) with the phagophore occurs upon or just after ONM fission, through interactions between Atg39, Atg11 and Atg8. Ultimately, autophagosomes containing double-membraned NDVs fuse with the vacuole, where nuclear cargo is degraded. TM, transmembrane domain. (Created with BioRender.com.)

more complete appreciation of the physiological significance of nucleophagy.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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Bacterial cell division: Orthogonal rotation is a convergent strategy

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Many rod-shaped bacteria divide at a fixed angle perpendicular to their long axis, while coccoid bacteria like *Staphylococcus aureus* rotate planes between generations. New research highlights the relationship between subtle asymmetry and division rotation in the understudied coccoid pathogen *Neisseria gonorrhoeae*.

Although cell growth requires the acquisition of resources, all cells rely on a fundamental process of significant loss for long-term success: cell division. Errors in division can be catastrophic, leading to inviable progeny, chromosome destruction, or lytic cell death. Because so much is at risk, division is coordinated to ensure the faithful partitioning of genetic material and cellular contents. For most bacteria, this involves the self-assembly of the tubulin homolog FtsZ into a Z-ring, marking the division site[1]. The Z-ring recruits the divisome, the conserved protein complex that drives cytokinesis

