JCB Journal of Cell Biology

SPOTLIGHT

Stress eating: Autophagy targets nuclear pore complexes

Angelina Sarah Gross[1] and Martin Graef[1,2]

Lee et al. (2020. *Nat. Cell Biol.* https://doi.org/10.1038/s41556-019-0459-2) and, in this issue, Tomioka et al. (2020. *J. Cell Biol.* https://doi.org/10.1083/jcb.201910063) describe the targeted degradation of nuclear pore complexes (NPCs) by selective autophagy, providing insight into the mechanisms of turnover for individual nucleoporins and entire NPCs.

Nuclear pore complexes (NPCs) constitute bidirectional gateways across the two lipid bilayers of the nuclear envelope (NE) and play critical roles in gene expression, cell division, and growth. They are massive assemblies of up to 500 proteins in which multiple copies of ∼30 mainly conserved nucleoporins (NUPs) organize into seven distinct subdomains (Fig. 1; 1, 2, 3). NPC malfunction has been linked to ageing and age-associated diseases such as Alzheimer's disease, cardiovascular diseases, and cancer. Given their essential function, it stands to reason that dedicated surveillance mechanisms would ensure NPC quality control. Intriguingly, NPC turnover differs between cellular states: in dividing and differentiated cells, nucleoporins are degraded in a mosaic manner with some nucleoporins being exceptionally long lived. In contrast, in quiescent cells, whole NPCs are turned over (4, 5). However, the mechanisms underlying the degradation of NPCs have remained elusive. Upon starvation or TORC1-inhibition, cells induce (macro)autophagy, a conserved degradative pathway, which results in the formation of double-membrane autophagosomes that engulf portions of the cytoplasm for degradation in the vacuole/lysosome (6). Under these conditions, Lee et al. and, in this issue, Tomioka et al. show in budding yeast that autophagy can selectively target whole NPCs and non-assembled nucleoporins representative of all seven NPC subdomains for degradation (1, 2).

Autophagy can target substrates in a selective manner, when the cargo or cargo-bound receptors physically interact with autophagy core machinery via the adaptor Atg11 (FIP200 in mammals) and the ubiquitin-like Atg8, covalently bound to the membranes of nascent autophagosomes (7). Tomioka et al. and Lee et al. show via genetic analyses in yeast that efficient degradation of nucleoporins depends on the presence of Atg11, indicating that selective autophagy, or NPC-phagy, mainly drives the turnover of NPCs. Moreover, Atg8 physically interacted with all tested nucleoporins in a manner that depends on the integrity of its Atg8 interacting motif (AIM) docking site (1, 2). The AIM docking site of Atg8 mediates the binding of proteins containing AIMs (7). Previously, autophagy receptors have been identified for the selective degradation of the nuclear ER (Atg39) and cortical/cytosolic ER (Atg40l; 8). Strikingly, individual or combined deletion of these receptors slowed NPC turnover but did not prevent it, suggesting the existence of additional and potentially specialized interactions for NPC recognition (1, 2). Tomioka et al. and Lee et al. discovered that Nup159, a nucleoporin within the cytoplasmic filaments of the NPC, contains an AIM required for the physical interaction of nucleoporins with Atg8. These data suggest that Nup159 may act as an inherent autophagy receptor for NPC turnover. In keeping with this notion, Lee et al. found that the presence of an Atg8-binding deficient Nup159 variant (Y1078A, L1081A) substantially reduced NPC turnover (1). In contrast, Tomioka et al. observed only a small decrease in the degradation of the same Nup159 variant, but not of other nucleoporins (2). Tomioka et al. propose that the AIM aides in the removal of non-assembled Nup159, a process they termed nucleoporinophagy, rather than in the degradation of whole NPCs (Fig. 1; 2). Additional physical interactions likely drive the efficient turnover of NPCs. First, Nup159 might contain other auxiliary AIMs similar to known autophagy receptors critically increasing the avidity of receptor-Atg8 interactions (1, 9). Second, and not mutually exclusive, concomitant interactions with other nucleoporins, Atg39/40, or as yet unknown receptors might drive NPC-phagy. Substrate recognition of NPCs by autophagy may involve complex and multilayered regulatory processes.

It remains to be seen how individual NPCs are destined for autophagic turnover. In favor of a nonstochastic process, yeast strains with defective NPC assembly displayed accelerated turnover rates of nucleoporins by autophagy (1, 2), suggesting that the assembly state of NPCs determines their recognition and degradation by autophagy.

[1]Max Planck Institute for Biology of Ageing, Cologne, Germany; [2]Cologne Excellence Cluster for Aging and Age-Associated Diseases, University of Cologne, Cologne, Germany.

Correspondence to Martin Graef: Martin.Graef@age.mpg.de.

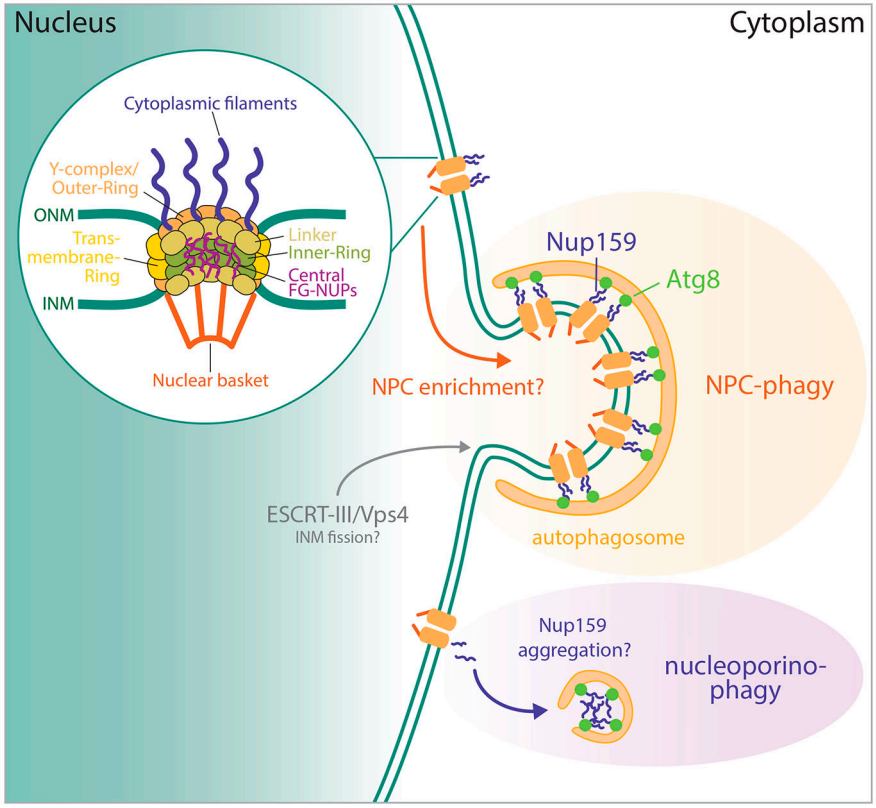

Figure 1. **Overview of the NPC structure and the two forms of autophagy targeting NPCs (NPC-phagy) and nucleoporins (nucleoporinophagy) for selective degradation.** For description, please see text.

Moreover, deficient assembly caused the clustering of NPCs within the NE (1), raising the possibility that sorting mechanisms may enrich defective NPCs in NE domains to facilitate their autophagic turnover. Indeed, Lee et al. observed that only NPC assembly mutants displaying NPC clustering also showed accelerated NPC-phagy, whereas mutants with compromised NPC assembly but no clustering exhibited dampened NPC turnover (1).

NPCs are embedded within the pores of the NE connecting the inner and outer nuclear membrane. This topology poses a challenge to the degradation of NPCs from the intact NE by autophagy (10). Intriguingly, using immuno- or correlative light and electron microscopy, both studies found that autophagosomes contain double-membrane vesicles carrying nucleoporins and seemingly enclosing nucleoplasm (1, 2). These data suggest that the NE undergoes significant membrane remodeling to generate vesicular NE fragments containing multiple NPCs that are targeted by autophagy (Fig. 1). How these NE-derived vesicles are generated without compromising nuclear function and whether their formation is coordinated with autophagosome biogenesis remains to be analyzed. Interestingly, NPC-phagy depended on Vps4 (1), raising the possibility that ESCRTIII/Vps4 contributes in its capacity to mediate inner nuclear membrane fission (11). Additionally, the mammalian ER-phagy receptors RTN3 and FAM134B drive ER membrane fragmentation by the means of oligomerization of their reticulon homology domains (12, 13). Notably, Atg40 also contains a reticulon homology domain and, as discussed before, accelerated NPC turnover by autophagy (1, 2, 8). Thus, it is tempting to speculate that, in coordination with ESCRTIII/Vps4-mediated inner nuclear membrane scission, Atg40 facilitates outer nuclear membrane fission to generate NPC-containing vesicles that are targeted by autophagy for degradation.

In summary, the work from Lee et al. and Tomioka et al. provide important insight into the mechanisms of NPC turnover by selective autophagy with broad implications for ageing and human diseases. Their initial description of this process raises exciting questions about the mechanisms and regulation of NPC-phagy, including the generation of NE-derived NPC vesicles.

Acknowledgments

This work was funded by the Max Planck Society and the Deutsche Forschungsgemeinschaft (SFB 1218 – Project number 269925409).

The authors declare no competing financial interests.

References

1. Lee, C.W., et al. 2020. *Nat. Cell Biol.* https://doi.org/10.1038/s41556-019-0459-2
2. Tomioka, Y., et al. 2020. *J. Cell Biol.* https://doi.org/10.1083/jcb.201910063
3. Beck, M., and E. Hurt. 2017. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/nrm.2016.147
4. Toyama, B.H., et al. 2019. *J. Cell Biol.* https://doi.org/10.1083/jcb.201809123
5. Toyama, B.H., et al. 2013. *Cell.* https://doi.org/10.1016/j.cell.2013.07.037
6. Melia, T.J., et al. 2020. *J. Cell Biol.* https://doi.org/10.1083/jcb.202002085
7. Gross, A.S., and M. Graef. 2020. *J. Mol. Biol.* https://doi.org/10.1016/j.jmb.2019.09.005
8. Mochida, K., et al. 2015. *Nature.* https://doi.org/10.1038/nature14506
9. Sawa-Makarska, J., et al. 2014. *Nat. Cell Biol.* https://doi.org/10.1038/ncb2935
10. Thaller, D.J., and C. Patrick Lusk. 2018. *Biochem. Soc. Trans.* https://doi.org/10.1042/BST20170442
11. Webster, B.M., et al. 2014. *Cell.* https://doi.org/10.1016/j.cell.2014.09.012
12. Grumati, P., et al. 2017. *eLife.* https://doi.org/10.7554/eLife.25555
13. Jiang, X., et al. 2020. *EMBO J.* https://doi.org/10.15252/embj.2019102608