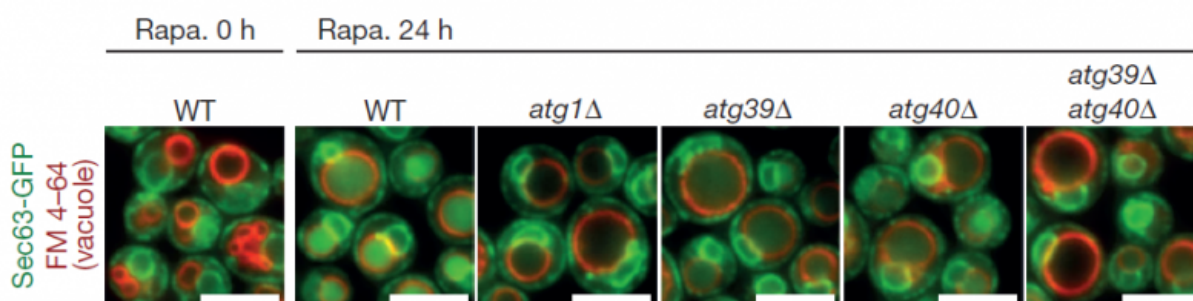


# New degradation proteins show route to cell survival

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Fluorescence microscopy images of yeast cells. Left to right: untreated wild type cells (Rapa. 0 h); cells treated with rapamycin for 24 hours (Rapa. 24 h) - wild type, *atg1* mutant, *atg39* mutant, *atg40* mutant and *atg39 atg40* double mutant. The researchers used the ER membrane protein Sec63 fused with green fluorescent protein (GFP) to monitor autophagy of the ER. Autophagic degradation of Sec63–GFP yielded vacuolar protease-resistant GFP fragments, which increased GFP fluorescence within the vacuole (red circles).

Studies by researchers at Tokyo Institute of Technology and colleagues reveal two proteins that induce degradation of certain cell constituents to help cell survival under nutrient-limiting conditions.

The degradation of cell constituents helps maintain the functions of the cell. This degradation process – '[autophagy](#)' – is linked to several

diseases. Although recent studies have suggested that selective autophagy targeted at specific cell constituents may also be responsible for maintaining healthy [conditions](#) in the cell – 'homeostasis' – the extent of these processes is unknown. Now researchers at Tokyo Institute of Technology, Yokohama City University and the Japan Science and Technology Agency have identified two new proteins that drive selective autophagy. They also show the role of these new autophagy pathways in preserving the cell in nutrient-limiting conditions.

The researchers focused their study on the yeast *Saccharomyces cerevisiae*. During selective autophagy, an autophagosomal membrane extends over the target through the binding of autophagy receptors to Atg8 proteins. By looking for proteins that bound to Atg8 in the yeast, Hitoshi Nakatogawa and colleagues identified two new autophagy [receptor proteins](#): Atg39 and Atg40.

The researchers noted that Atg39 and Atg40 levels increased in the presence of the chemical rapamycin, which mimics nitrogen starvation. Further studies linked the two proteins to autophagy of a certain cell constituent – the endoplasmic reticulum (ER), a network of flattened membrane enclosed sacks – in nitrogen-starved conditions. The same conditions also triggered degradation of a part of the nucleus by Atg39; this protein localized to a special part of the ER surrounding the nucleus. Atg40 localized to other ER regions and mediated their degradation. Blocking nucleus degradation by Atg39 led to cell death in nitrogen-starved conditions. Atg40 was suggested to correspond to a human protein encoded by FAM134B, a causative gene for a hereditary sensory and autonomic neuropathy.

"Our results provide fundamental insight into the pathophysiological roles and mechanisms of 'ER-phagy' and 'nucleophagy' in other organisms," explain the researchers in their report of the work. Further studies are required to determine the ER components that must be

degraded as well as whether the purpose of this autophagy process is removal of material or making substances available through the breakdown.

## **Autophagy**

The term autophagy derives from the Greek auto-, "self" and phagein, "to eat" and refers to processes that lead to the degradation of cell constituents. A double membrane encloses the constituent, separating it from the rest of the cell. The constituent is then broken down into simpler chemical substances.

The process can improve [cell survival](#) under starvation conditions by recycling cell material and maintaining energy levels. It can also help survival by allowing organisms to adapt to stresses imposed by disease. Alternatively disease-induced autophagy may diminish the health and survival of the afflicted organism.

## **Discovering autophagy receptor proteins**

*Saccharomyces cerevisiae* is the yeast responsible for fermentation in baking, brewing and winemaking. It has been intensively studied and used as the model for studies leading to the discovery of many proteins involved in cell cycles and signalling.

The known role of Atg8 in the double membrane encapsulation of cell constituents to be degraded led the researchers to look for proteins that bind to Atg8 in *S. cerevisiae*. They used mass spectrometry of Atg8 immunoprecipitates and identified the proteins, Ylr312c and Yor152c, which they named Atg39 and Atg40, respectively.

## **The role of Atg39 and Atg40**

Previous work had shown that the endoplasmic reticulum (ER) was efficiently degraded in nitrogen-starved conditions. The researchers tagged the ER with green fluorescent [protein](#) so they could track it and found that knock out of either Atg39 or Atg40 partially blocked the ER autophagy process in low-nitrogen conditions, while knock out of both almost blocked it entirely.

Further studies also showed that Atg39 led to [degradation](#) of nuclear components – nucleophagy. The researchers observed abnormal nuclear morphology in atg39 mutants, which were less viable than wild-type cells under a lack of nitrogen. They suggest the atg39 mutant [cells](#) become more susceptible to cell death under nitrogen-deprived conditions due to an inability to perform nucleophagy.

Although selective autophagy of the ER under nitrogen-starved conditions was significantly blocked by Atg40 knock out, the viability of the cell was not reduced. The [researchers](#) suggest that Atg40-mediated ER-phagy becomes critical under alternative conditions.

**More information:** "Receptor-mediated selective autophagy degrades the endoplasmic reticulum and the nucleus." *Nature* [DOI: 10.1038/nature14506](#)

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