

Scientists Use AI to Map How Nearly Every Yeast Gene Controls Cellular Recycling

A genome-wide study combining time-lapse imaging and deep learning reveals the hierarchical network controlling autophagy, offering a level of insight that was previously beyond experimental reach. The findings have implications for cancer, neurodegeneration, and aging.

OSLO, NORWAY — Researchers at Oslo University Hospital and the University of Oslo have created the most detailed map so far of how the genome regulates autophagy, the process cells use to break down and recycle their own components. The findings are published in the journal ***Nature Cell Biology***.

By combining high-content fluorescence microscopy with deep learning, the team analyzed **5,919 yeast gene mutants**, covering about 90 percent of the yeast genome. The researchers tracked how autophagy changed over time as cells moved through periods of nutrient starvation and recovery.

Autophagy plays a central role in cellular maintenance. It clears damaged proteins and worn-out organelles and its dysregulation is linked to cancer, Parkinson's disease, Alzheimer's disease, and metabolic disorders. Despite decades of research identifying many of the core genes involved, the broader regulatory system controlling autophagy timing and magnitude has remained poorly understood.

To investigate this, the researchers used an arrayed mutant library and imaged the cells every hour during a 19-hour starvation and recovery experiment. They then trained a deep neural network to classify individual cells and measure how autophagy changed over time for each gene mutant. The resulting online available dataset, compiled into a resource called **AutoDRY**, captures key aspects of autophagy dynamics: how quickly the process switches on, how efficiently it shuts off, and how well autophagosomes form and are cleared.

Key findings include:

Hierarchical control: Regulatory genes are organized in layers. Some act as high-level controllers that shape the overall autophagy response, while others fine-tune specific stages of the process.

Phase-dependent regulation: Different groups of genes control autophagy during starvation and during recovery, indicating temporally separate regulatory programs.

New regulators: The screen uncovered previously uncharacterized genes influencing autophagy dynamics, expanding the regulatory landscape beyond the classic ATG gene family.

Predictive modeling: The quantitative profiles allow genome-scale predictions of how genetic or pharmacological perturbations may alter autophagy dynamics.

Implications for Human Disease and Drug Discovery

Because autophagy machinery is highly conserved from yeast to humans, the regulatory principles identified here are likely to translate directly to human cell biology. The identification of upstream regulators that influence the timing and strength of the entire autophagy response highlights potential new targets for drugs aimed at diseases where autophagy is overactive or insufficiently active.

In cancer, for instance, tumour cells often hijack autophagy to survive chemotherapy and nutrient deprivation. In neurodegeneration, insufficient autophagy can allow toxic protein aggregates to accumulate. Understanding which genes control specific phases of the process could help researchers design drugs that either suppress or stimulate autophagy more precisely and with fewer off-target effects.

Beyond autophagy itself, the AutoDRY project demonstrates a broader strategy for studying dynamic cellular processes. By combining systematic genetics, time-resolved imaging, and machine learning, the same approach could be used to map genome-scale control of other processes such as DNA damage repair or cell division.

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AutoDRY: <https://cancel-apps.medisin.uio.no/AutoDRY/>

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