Assembly Required

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RESEARCH

Connections Made Among Branches of Cell Recycling System

Every cell in the body is equipped with quality-control mechanisms to eliminate damaged components and maintain a balance among those that are needed. One such mechanism is autophagy, a process in which the cell actually eats itself from within, engulfing unwanted parts and degrading and recycling them for higher priority uses.

Years of research in simple organisms such as yeast have uncovered autophagy's basic mechanisms, but this work may have missed the forest for the trees. Now a team from HMS has mapped broader territory by charting the overall organization of the autophagy system. Defects in the system can wreak havoc with normal body processes and are known to play a role—not yet completely understood—in cancer and neurodegenerative disorders.

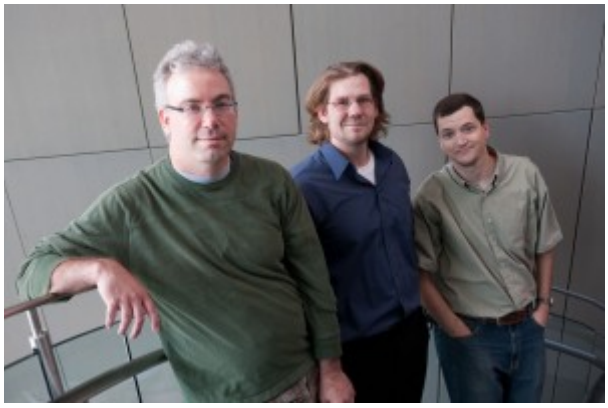

Photo by Suzanne Camarata

From left, Wade Harper, Mathew Sowa, Steven and Christian Behrends have mapped out connections within the cell's recycling center.

Using methods to delineate protein–protein interactions on a finer scale than was previously possible, Wade Harper, the Bert and Natalie Vallee professor of molecular pathology at HMS, and his colleagues analyzed proteins known to be involved in autophagy to find out whether individual components of the autophagy pathway communicated with one another. Autophagy, like other signaling systems in the body, involves assemblies of proteins that interact to form a network, said Harper.

The researchers created a detailed map of many of the subnetworks that make up the autophagy interaction network. They also identified new interactions between proteins in different subnetworks.

“The significance of this is that various arms of the autophagy system seem to communicate with each other,” said Harper, presumably allowing coordination of the overall pathway. The study, whose co-authors are postdoctoral fellows Christian Behrends and Mathew Sowa in the Harper lab and Steven Gygi, an HMS associate professor of cell biology, appeared online June 20 in the journal *Nature*.

Break to Rebuild

Autophagy is involved in many basic biological processes, including development, aging and cell turnover. During autophagy, components of the cell are sequestered within a membrane and delivered to an organelle called the lysosome, where they are degraded. In most cells, autophagy is an ongoing process that clears away damaged organelles, misfolded proteins and even infectious agents that make it past the cell membrane.

The autophagy system is particularly important when cells are starved of nutrients. When a lack of nutrients is detected, the system works overtime to degrade proteins, freeing up the amino acids from which they are made for use in life-saving processes.

“Understanding how autophagy controls cell survival in response to nutrient deprivation or under various physiological conditions is an important area of research,” said Harper.

For the autophagy network to run smoothly, a large number of signaling, membrane and scaffolding proteins must be recruited and coordinated. Pathways that interpret the stores of nutrients, amino acids and growth factors available to the cell control the autophagy system.

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—Wade Harper

A Permanent Circuit

A key player in the system is the molecule mTOR, or mammalian target of rapamycin. mTOR is an enzyme that influences the action of other proteins and is known to regulate the autophagy process. When mTOR is active, autophagy is reduced. Harper and his colleagues used an mTOR inhibitor to turn on autophagy, then examined how the network was altered.

“It could have been the case that in the absence of autophagy, the components are disassembled, and any autophagy stimulus would then lead to a dynamic assembly,” said

Harper. Instead, many of the complexes appeared to be largely preassembled. “In essence, this means that the system is hardwired for activation,” he said.

The next step for Harper and his colleagues will be to identify specific actions of various autophagy subnetworks. By describing the details of the autophagy network at each step of the process, they hope to find points at which drugs can be used to intervene in disease development.

The researchers hope their work will serve as a resource for other scientists studying this pathway and lead to more experiments and therapeutic applications. Molecules that can regulate or inhibit autophagy have the potential to treat neurodegenerative diseases, cancerous tumors and diseases associated with aging. Among the findings reported in the paper, Harper said, are several new candidate drug targets.

—Mary Bates

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