AUTHOR COMMENTARIES - From Special Topics

Autophagy - July 2009
Interview Date: September 2009

PDF

Yoshinori Ohsumi

From the Special Topic of Autophagy

*According to our Special Topics analysis of autophagy research over the past decade, the work of Professor Yoshinori Ohsumi ranks at #1 by total number of papers and #2 by total cites, based on 93 papers cited a total of 7,061 times. Five of these papers are among the most-cited over the past decade for the topic. In Essential Science Indicators*SM *from Thomson Reuters, Prof. Ohsumi's record includes 115 papers cited a total of 7,436 times between January 1, 1999 and April 30, 2009.*

Prof. Ohsumi started his autophagy work at the Tokyo University, then moved to the National Institute of Biology, Okazaki, and now belongs to the Tokyo Institute of Technology's Integrated Research Institute.

Below,* ScienceWatch.com *talks with Prof. Ohsumi about his highly cited research.

SW: Would you tell us a bit about your educational background and research experiences?

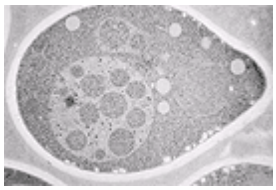
I started graduate school at Tokyo University under the guidance of Professor Kazutomo Imahori. Since the first subject I started to work with was *in vitro* protein biosynthesis of *E. coli*, intracellular dynamics of proteins has always been in my mind. From the third grade I changed my research subject to the mode of action of Colicin E3, which turned out to inactivate ribosomes after binding to the cell surface receptor. Gradually I became interested in membrane phenomena.

Then I became a postdoc at Dr. G.M. Edelman's lab at Rockefeller University for three years. I failed to get any satisfactory results, but learned something in cell biology, and strangely enough I started yeast work in his lab.

Then I came back to Japan and worked with Prof. Yasuhiro Anraku. His whole lab had been working on amino acid transport in *E. coli*, while I started biochemical studies on vacuolar membranes. By establishing a method of vacuolar membrane vesicle preparation, I could show the vacuolar membrane possesses active transport systems of amino acids and ions. We also succeeded in showing that the vacuolar type H+-ATPase was a primary pump for proton gradient across the vacuolar membrane. I realized that the vacuole is a much more active organelle then ever thought and plays important roles in maintaining intracellular homeostasis.

SW: What first interested you in autophagy?

In 1988 I moved to College of Arts and Sciences at the University of Tokyo as an associate professor. It was a small lab—just me and several instruments. At that time I decided to study a lytic function of vacuoles as my main research theme. Nothing was known about what and how cellular proteins are degraded in this acidic compartment. It was hard to get a clear strategy from where I should start. In the life cycle of yeast, sporulation is a dramatic cell differentiation process, which is triggered by depletion of the nitrogen source from the environment. So I thought bulk protein degradation must occur to this cell remodeling.



3 hrs nitrogen-starved cells

View/download five accompanying slides and descriptions.
PDF

At that time not many people had observed inside the yeast cell by light microscope, though now fluorescence microscopic observation is quite popular for yeast researchers. The vacuole in yeast is the only organelle easily detectable under light microscope, so I had always observed them this way. One simple idea stuck me. If vacuolar proteinase-deficient mutant cells are shifted by the condition of nitrogen starvation, I might see some structures inside the vacuole which had escaped from degradation. In fact, this proved to be the case. I found such clear and impressive morphological changes of the vacuole. Many vesicles, named autophagic bodies, were vigorously moving around in the vacuole. This was the just the starting point of my work on autophagy in yeast. It was quite natural that I started to introduce genetic screening to get autophagy-defective mutants by microscopy again.

SW: Much of your highly cited work appears to focus on various Apg proteins. Would you talk about this aspect of your research, and tell us why Apg seems to be a key player in autophagy?

Our first screen was quite efficient and we could get 14 APG genes essential for autophagy. Our Apg (now renamed as Atg) proteins appeared to consist of molecular machinery of autophagosome formation, which was the most critical event of autophagy. I personally believe that nutrient deficiency is the most frequent and serious stress for wildlife. In nature, an organism needs to maintain viability against nutrient deficiency, therefore a recycling system of its own constituents must be a fundamental requirement of life. Therefore, starvation-induced autophagy is the origin of autophagy in the evolution of eukaryotes. In the future we will have much more factors required for autophagy in various physiological circumstances, but the core machinery consisting of these Atg proteins must play important roles for membrane dynamics.

We know now that these Atg proteins consist of five functional units including two ubiqutin-like conjugation systems. Autophagy became quite a popular field in biology, but still not so many people are working on the molecular mechanism of membrane dynamics during autophagy. I believe several basic questions about membrane dynamics still remain. Therefore my group is challenging these mysteries by concentrating on the simplest system, yeast, *S. cerevisiae*.

SW: Earlier this year, you published a paper in *Biochemical and Biophysical Research Communications*, "Lap3 is a selective target of autophagy in yeast, *Saccharomyces cerevisiae*." Could you tell our readers something about this paper?

"I personally believe that nutrient deficiency is the most frequent and serious stress for wildlife."

We thought that starvation-induced autophagy is a non-selective process of degradation. Standard medium of yeast, YEPD, is extremely rich in nitrogen compounds and other nutrients. The cells growing in this medium are adjusted to rapid growth and lack completely autophagy, which may be a rather unusual situation in nature. So far we found Ald6 is preferentially delivered into the vacuole to be degraded. It is the obvious question for us whether yeast cells also have a selective and constitutive mode of autophagy, which is crucial for such systems as neuronal cells in mammals. We found Lap4 behaves quite similarly with Ape1(Lap3), main target of the Cvt pathway, but it is not a vacuolar resident but rather degraded in the vacuole.

We are interested in what kind of growth conditions induce selective mode of autophagic degradation of cytoplasmic soluble enzymes, ribosomes, and organelles. These studies will give clues to understand the various modes of autophagy in mammals and plants.

How has our knowledge of autophagy changed over the past decade?

Autophagy was discovered quite a long time ago by excellent electron microscope work, but quite little was known about the physiological roles of autophagy. Identification of ATG genes tremendously changed the studies of autophagy. The effect of ATG gene disruption revealed

vast involvements of autophagy in various aspects of life. Now there is increasing consensus that cellular proteins are in dynamic states between synthesis and degradation.

Where would you like to take your research on autophagy in the next decade?

With the field getting more crowded, I doubt that I myself will be able to settle so much broad aspects of problems related to autophagy in the next few years. As mentioned above, there are so many problems that remain to be solved in membrane dynamics of autophagy, especially formation of autophagosome and various modes of autophagy, which are at present called collectively autophagy, but I think it is necessary to dissect them according to molecular mechanism.

Yoshinori Ohsumi, Ph.D., Professor
Tokyo Institute of Technology
Integral Research Institute (IRI)
Nagatsuda, Midori-ku, Yokohama, Japan

Yoshinori Ohsumi's current most-cited paper in *Essential Science Indicators*, with 757 cites:

Kabeya Y, *et al.*, "LC3, a mammalian homologue of yeast Apg8p, is localized in autophagosome membranes after processing," *EMBO J.* 19(21): 5720-8, 1 November 2000. Source: *Essential Science Indicators* from Thomson Reuters.

KEYWORDS: AUTOPHAGY, PROTEIN INTRACELLULAR DYNAMICS, MEMBRANE PHENOMENA, YEAST, S. CEREVISIAE, E. COLI, VACUOLAR MEMBRANE VESICLES, ACTIVE TRANSPORT SYSTEMS, PROTON GRADIENT, VACUOLE, BULK PROTEIN DEGRADATION, NITROGEN STARVATION, GENETIC SCREEN, APG, ATG, LAP3, LAP4.

PDF

back to top

Special Topics : Autophagy : Yoshinori Ohsumi Interview - Special Topic of Autophagy

Science Home | About Thomson Reuters | Site Search