AUTHOR COMMENTARIES - From Special Topics

Autophagy - July 2009
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Noboru Mizushima
From the Special Topic of Autophagy

According to our Special Topics analysis of autophagy research over the past decade, the scientist whose work ranks at #1 by total citations is Dr. Noboru Mizushima, based on 82 papers cited a total of 7,376 times. Eleven of these papers are also ranked among the most-cited over the past decade and over the past two years.

In Essential Science Indicators℠ *from Thomson Reuters, Dr. Mizushima's work, which is largely classified in the fields of Molecular Biology & Genetics and Biology & Biochemistry, includes 92 papers cited a total of 7,628 times between January 1, 1999 and April 30, 2009.*

At present, Dr. Mizushima is a Professor in the Department of Physiology and Cell Biology at Tokyo Medical and Dental University. In 2007, he won the FEBS Letters *Young Scientist Award.*

In the interview below, ScienceWatch.com *talks with Dr. Mizushima about his work in autophagy.*

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

I graduated from the School of Medicine at Tokyo Medical and Dental University in 1991, and finished the internal medicine residency program in 1993. I started my research career with studies on molecular immunology and received a Ph.D. in 1996. After that, I joined Dr. Yoshinori Ohsumi's laboratory at the National Institute for Basic Biology as a postdoctoral fellow, where I worked for seven years on the molecular mechanism and physiological role of autophagy in yeast and mammals. In 2004, I established my own laboratory at the Tokyo Metropolitan Institute of Medical Science and then, in 2006, I joined Tokyo Medical and Dental University as a professor of physiology and cell biology.

SW: What first interested you in autophagy?

Soon after I received my Ph.D., I happened to read a short Japanese review article by Dr. Ohsumi. At that time, Dr. Ohsumi had already isolated autophagy-defective (apg) yeast mutants and identified some autophagy-related genes based on the apg mutants. What fascinated me in the article was that all of them were new genes whose functions were not easily determined by their amino acid sequences. Although autophagy is conserved in all eukaryotes, molecular biological studies were very limited.

Inspiration hit me that the studies on yeast autophagy might lead to mammalian autophagy. Thus, I joined Dr. Ohsumi's laboratory and studied the molecular mechanism of yeast autophagy. It was very lucky

for me to discover a unique ubiquitin-like conjugation system required for autophagy, which is now called the Atg12 conjugation system.

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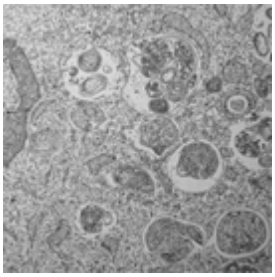

Autophagosomes in starved fibroblasts.

Photo by Drs. Chieko Kishi and Noboru Mizushima

SW: One of your highly cited papers in our analysis is the 2001 *Journal of Cell Biology* paper, "Dissection of autophagosome formation using Apg5-deficient mouse embryonic stem cells." Would you tell us about this paper, and why you think it's so highly cited?

Although autophagy was first discovered in mammalian cells in 1960s, molecular studies on mammalian autophagy have been very limited. During our analysis of yeast autophagy, we soon realized that most of the yeast autophagy genes are well conserved in higher eukaryotes. I therefore generated mouse embryonic stem cells in which a critical autophagy gene was deleted (Atg5-/- cells). In this 2001 *JCB* paper, we reported function of Atg5 in autophagosome formation and demonstrated live images of autophagosome formation for the first time using GFP-tagged Atg5.

Furthermore, since this was the first mammalian cell line whose autophagic activity was completely suppressed, many researchers have used this cell line to analyze the role of autophagy in cultured cells. Using the embryonic stem cells, we later generated Atg5-/- mice, with which we have discovered several important roles of autophagy in mice (Kuma *et al.* 2004, Hara *et al.* 2006, and Tsukamoto *et al.* 2008).

SW: Another of your highly cited papers is the 2004 *Molecular Biology of the Cell* paper, "*In vivo* analysis of autophagy in response to nutrient starvation using transgenic mice expressing a fluorescent autophagosome marker." Please tell us about this paper - its aims, methods, and findings.

At that time, the role of autophagy in mammals was still poorly understood. Moreover, we did not exactly know where and when autophagy is induced *in vivo*, largely because methods for monitoring autophagy were limited and unsatisfactory. The most standard method was conventional electron microscopy. However, this method requires considerable skill and a lot of time, and sometimes it is difficult to distinguish autophagic vacuoles from other structures just by morphology.

To monitor autophagy simply and accurately, we generated a transgenic mouse systemically expressing GFP-LC3 that labels autophagosomes. Using this transgenic mouse, we can now detect autophagosomes in every tissue easily by fluorescent microscopy. We have observed that autophagy is induced in almost all tissues except the brain following starvation. We also used this mouse model in later papers, in which we found that autophagy is activated after birth (Kuma et al. 2004) and fertilization (Tsukamoto *et al*. 2008). And now more than 300 laboratories use this autophagy-indicator mouse model.

SW: Earlier this year, you published a paper in the January 2009 issue of *Autophagy*, "Role of ULK-FIP200 complex in mammalian autophagy FIP200, a counterpart of yeast Atg 17?" Could you tell our readers something about this paper?

Autophagy-related genes are well conserved from yeast to mammals. However, recent studies have identified several mammalian-specific autophagy genes. One of them is FIP200, which is discussed in this short review. FIP200, also known as RB1CC1, has several previously known functions such as in cell adhesion, cell-cycle regulation, and RB gene expression. We also discovered that FIP200 is essential for autophagy. One interesting thing is that FIP200 has no apparent homology to any known yeast Atg proteins, although its function may be similar to yeast Atg17. We also found Atg101, which is absent in yeast. These studies imply that although autophagy machinery seems to be conserved from yeast, mammals may have their own additional mechanism.

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

The autophagy research field has dramatically changed during the past decade. A lot of autophagy-specific molecules have been identified in various species, including humans. In addition to the well-known role of autophagy as a starvation adaptation response, many unexpected roles of autophagy have been discovered. For example, autophagy turned out to be important for neonatal survival, preimplantation development, prevention of neurodegeneration, killing of intracellular microorganisms, antigen presentation, tumor suppression, anti-aging, etc.

"...although autophagy machinery seems to be conserved from yeast, mammals may have their own additional mechanism."

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

One remaining important issue is that how autophagy is regulated within cells and in whole animals. We have recently published that mTOR directly regulates the autophagy factors, but upstream signaling is not very clear. Furthermore, although it has been suggested that insulin is a major regulatory factor of autophagy *in vivo*, contribution of other hormones mostly remains unclear.

Another topic would be organelle turnover. Since organelles are too big to be degraded by proteasomes, autophagy should be very important. Recent studies have shown that autophagy can selectively degrade some proteins and organelles. Studies of organelle turnover will be also important for understanding of pathogenesis of human diseases, such as Parkinson's disease, in which mitochondrial quality control is reported to be critical.

SW: What would you say the "take-home message" about your work should be?

Protein turnover may be one of the old topics in life science research, but there are still a lot of interesting things that have remained undiscovered. Another thing that I would like to emphasize is that all these important findings were brought to us following the breakthrough experiments using yeast cells. Yeast genetics is still a powerful tool in biomedical research.

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Noboru Mizushima'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, YEAST, APG, MAMMALS, ATG12 CONJUGATION SYSTEM, ATG5, TRANSGENIC MICE, IN VIVO, AUTOPHAGY GENES.

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