

- [ScienceWatch Home](#)
- [Inside This Month...](#)
- [Interviews](#)

- [Featured Interviews](#)
- [Author Commentaries](#)
- [Institutional Interviews](#)
- [Journal Interviews](#)
- [Podcasts](#)

Analyses

- [Featured Analyses](#)
- [What's Hot In...](#)
- [Special Topics](#)

Data & Rankings

- [Sci-Bytes](#)
- [Fast Breaking Papers](#)
- [New Hot Papers](#)
- [Emerging Research Fronts](#)
- [Fast Moving Fronts](#)
- [Corporate Research Fronts](#)
- [Research Front Maps](#)
- [Current Classics](#)
- [Top Topics](#)
- [Rising Stars](#)
- [New Entrants](#)
- [Country Profiles](#)

About Science Watch

- [Methodology](#)
- [Archives](#)
- [Contact Us](#)
- [RSS Feeds](#)

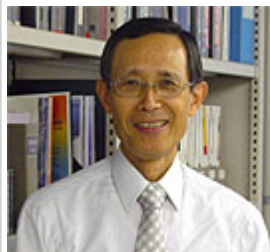

[Interviews](#)
[Analyses](#)
[Data & Rankings](#)

Special Topics : Autophagy : Eiki Kominami Interview - Special Topic of Autophagy

AUTHOR COMMENTARIES - From Special Topics

Autophagy - July 2009

Interview Date: December 2009



Eiki Kominami

From the Special Topic of [Autophagy](#)

In our Special Topics analysis on autophagy research over the past decade, the work of Dr. Eiki Kominami ranks at #5 by total number of papers, #6 by total number of citations, and #11 by citations per paper, based on 51 papers cited a total of 3,245 times.

*In [Essential Science IndicatorsSM](#) from [Thomson Reuters](#), Dr. Kominami's record includes 115 papers, the majority of which are classified under either *Biology & Biochemistry* or *Molecular Biology & Genetics*, cited a total of 5,112 times between January 1, 1999 and August 31, 2009. Dr. Kominami is an Emeritus Professor and President of Juntendo University in Tokyo, Japan.*

In the interview below, he talks with ScienceWatch.com about his highly cited research.

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

My M.D. was conferred from Okayama University in 1968. After clinical training as a resident in gastroenterology at Okayama University Hospital for several years, I decided to enter the path to live as a scientist and got a Ph.D. in medicine at Tokushima University in 1975. I worked for two years (1978-1979) as an assistant professor at the Biochemical Institute of Freiburg University, West Germany.

After returning to Japan in 1980, I worked as an associate professor at Tokushima University Institute for Enzyme Research. In 1988, I landed a professorship in the Department of Biochemistry at Juntendo University, School of Medicine, and served out a term until reaching retirement in March, 2009. I have currently been the President of Juntendo University since 2008.

SW: What first interested you in autophagy, and is there a specific aspect of autophagy research on which you focus?

When I was at Tokushima University from 1980 to 1988, my interest in biochemical studies was the regulation of lysosomal proteolysis. In 1984 there was a report in the Annual Meeting of the Japanese Biochemical Society about an isolation method for autolysosomes from livers of leupeptin-treated rats. Using this technique, I found that many proteins from cytosol and various organelles are incorporated into autolysosomes non-selectively in starved rats.

I am now interested in how autophagy or autophagy machinery is involved in metabolic regulation of various organs via lysosomal hydrolysis, including proteolysis, and how dysregulation of autophagy occurs in

various pathological conditions.

SW: One of your most-cited papers in our analysis is the 2006 *Nature* article, "Loss of autophagy in the central nervous system causes neurodegeneration in mice," (Komatsu M, *et al.*, 441[7095]:880-4, 15 June 2006). Would you talk a little bit about this paper, its findings, and why it is so highly cited?

In 2005, a year before the publication of this *Nature* article, our group published the first paper concerning autophagy-deficiency in mouse liver (Komatsu M, *et al.*, "Impairment of starvation-induced and constitutive autophagy in ATG7-deficient mice," *J. Cell Biol.* 169[3]: 425-34, 9 May 2005). Phenotype analyses revealed some characteristics of autophagy-deficient liver, many of which were well understood as a direct effect of autophagy impairment: marked accumulation of cell proteins occurred as a result of loss of autophagic proteolysis, which eventually resulted in hepatomegaly accompanying significant inflammatory responses. Unexpectedly, numerous ubiquitin-positive aggregates were found to accumulate in autophagy-deficient hepatocytes. As autophagy deficiency did not affect the proteolytic activities of ubiquitin-proteasome system, this unique phenotype attracted our attention.

We then decided to create brain-specific autophagy-deficient mice to compare the phenotype of autophagy-deficient brain with that of autophagy-deficient liver. Surprisingly, these brain-specific autophagy-deficient mice exhibited behavioral defects including abnormal limb-clasping reflexes and disability in coordinate movements. These symptoms are typically observed in various neurodegenerative diseases such as Alzheimer's disease, Huntington's disease and Parkinson's disease. Our report clearly demonstrated for the first time that autophagy significantly contributes to maintaining cell health by degrading aged or damaged cytoplasmic components.

In this respect, our findings have drawn considerable attention, which is the most likely reason for many citations of this paper. Of course, we could confirm that many ubiquitin-positive aggregates were also present in autophagy-deficient brain, supporting that the accumulation of ubiquitylated proteins is a common phenotype of autophagy deficiency.

SW: Last year, your group published a paper in *Autophagy*, "Loss of Pten, a tumor suppressor, causes the strong inhibition of autophagy without affecting LC3 lipidation," (Ueno T, *et al.*, 4[5]: 692-700, 1 July 2008). Could you tell our readers something about this paper?

Using a cultured cell system, it has been previously reported that active class III-phosphatidylinositol 3-kinase complex is essential for autophagy, whereas activation of class I phosphatidylinositol 3-kinase causes autophagy suppression. Pten (phosphatase and tensin homolog deleted on chromosome ten), a tumor suppressor, functions as a negative regulator of the class I phosphatidylinositol 3-kinase/Akt pathway, thus antagonizing insulin-dependent cell signaling. Hepatocyte-specific Pten-deficient mice created by one of our collaborators' groups were a useful experimental system for investigating the effects of hyper activation of the class I PI3-kinase/Akt pathway on cell metabolism.

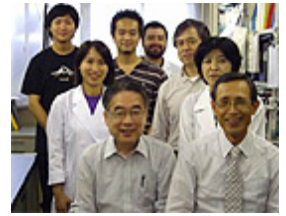
"As autophagy deficiency did not affect the proteolytic activities of ubiquitin-proteasome system, this unique phenotype attracted our attention."

The targeted deletion of Pten in mouse liver leads to insulin hypersensitivity and the upregulation of the phosphatidylinositol 3-kinase/Akt signaling pathway with elevated levels of phosphorylated Akt and the development of adenomas and hepatocellular carcinomas. We extensively investigated these conditional knockout mice and found that hepatic autophagy was markedly suppressed. The autophagy suppression was mainly attributable to the inhibition of autophagosome formation, although the loss of Pten did not affect the autophagy-specific protein conjugation reaction to form Atg12-Atg5 and LC3-II.

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

I should say that our knowledge of autophagy has been tremendously increased or enlarged during the past 10 years. The article published in *Nature* by Mizushima *et al.* in 1998 ("A protein conjugation system essential for autophagy," 395[6700]: 395-8, 24 September 1998) surprised many cell biologists who had been engaged in the study of autophagy as well as other cellular protein degradative systems in that a unique protein conjugation system similar to that of ubiquitin proteasome plays an indispensable role in autophagy. The paper certainly became an epoch-making landmark in the history of autophagy, not because it solved difficult questions of autophagy in a single burst (the ATG conjugation system still remains the Gordian knot of autophagy), but because it clearly demonstrated which of the ATG genes play in the center.

[+] enlarge



Eiki Kominami's team

This work hinted at gene-knockout approaches that have become a royal road to understanding physiology and pathology of autophagy. One can easily recognize that diverse functions of autophagy, including roles in cytoplasmic quality control, metabolic compensation, innate immunity, cell-defense against microbial infection, etc., have been elucidated during the subsequent 10 years. Many findings have been accomplished using ATG-gene knockout mice, flies, and *C. elegans*.

SW: Why is it important to study autophagy?

Autophagic functions are broadly associated with various pathologies such as cancer, neurodegeneration, cardiac disease, diabetes, and infections. New insights into the molecular mechanisms of autophagy could lead to a discovery of potential drug targets. However, autophagy is a fundamental homeostatic process and an essential cell-protective mechanism. An important issue of medicine in the 21st century is how to prevent diseases, rather than fight against them. I believe that the more insights we can obtain into the mechanism of autophagy, the more procedures we can get to keep us healthy and prolong a life span. For example, it's known that autophagic activities at the individual level decline along with aging. Creating medicine to stimulate autophagy will bring us more peaceful and pleasant days at our older age. ■

Eiki Kominami, M.D. & Ph.D.

President

Juntendo University

Tokyo, Japan

Eiki Kominami's current most-cited paper in *Essential Science Indicators*, with 843 cites:

Kabeza 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, LYSOSOMAL PROTEOLYSIS, AUTOLYSOSOMES, LIVER, METABOLIC REGULATION, LYSOSOMAL HYDROLYSIS, DYSREGULATION, UBIQUITIN-PROTEASOME SYSTEM, AUTOPHAGY-DEFICIENT BRAIN, PTEN, LC3 LIPIDATION, PHOSPHATIDYL-INOSITOL 3-KINASE/AKT SIGNALING PATHWAY, CELLULAR PROTEIN DEGRADATIVE SYSTEMS, PROTEIN CONJUGATION SYSTEM.

 PDF

[back to top](#) 

Special Topics : Autophagy : Eiki Kominami Interview - Special Topic of Autophagy

[Science Home](#) | [About Thomson Reuters](#) | [Site Search](#)

[Copyright](#) | [Terms of Use](#) | [Privacy Policy](#)