

Alternative autophagy pathways conserved from yeast to mammals

Shigeomi Shimizu

Professor of Pathological Cell Biology at TMDU

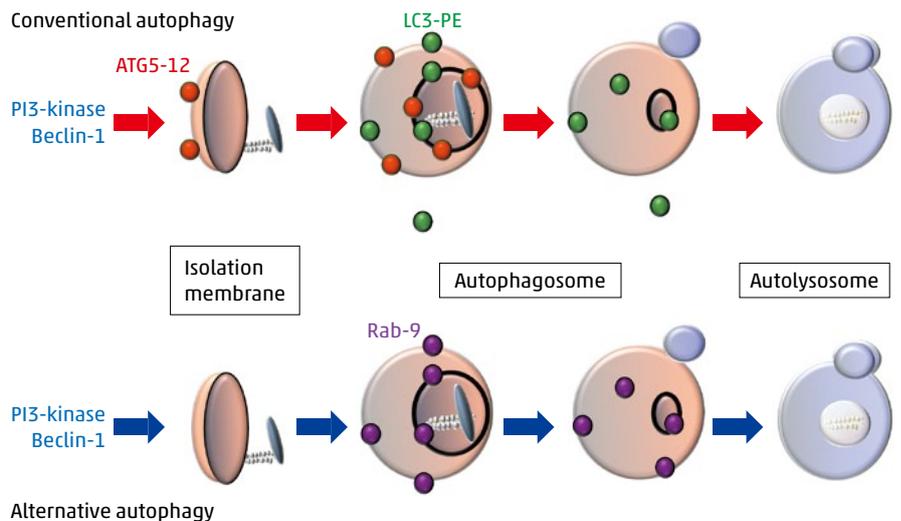
Q Can you explain the importance of autophagy to a cell?

A: Autophagy involves the breakdown of unwanted or damaged cellular contents through digestion within autolysosomes using lysosomal hydrolytic enzymes. It is a protective mechanism that is activated when the cell is stressed by damage to DNA or organelles, or following nutrient starvation. In addition to removing damaged proteins, or even whole organelles, it can also help to regulate protein expression levels by low-level constitutive autophagy.

Q You have identified an alternative autophagy process. How does this differ from the conventional system?

A: Autophagy occurs through the actions of more than 30 proteins, including Atg5 and Atg7, which are highly conserved from yeast to mammals. However, together with my many outstanding colleagues at TMDU and other fine Japanese institutions, we noticed that mammalian cells lacking Atg5 and Atg7 were healthy and still able to undergo autophagy-mediated protein degradation, controlled by Ulk1 protein rather than Atg5/Atg7. This happened when the cells were severely stressed by DNA damage rather than nutrient deprivation. Although the structures involved in this alternative autophagy exactly resemble those of conventional autophagy, they have different functions and can degrade different subcellular components. For example, in the maturation process of red blood cells, reticulocytes lose organelles such as mitochondria to become erythrocytes (the mature cell). My

Schematic model of autophagy



There are at least two modes of autophagy, *i.e.* conventional and alternative autophagy. Conventional autophagy depends on Atg5 and Atg12 and is associated with LC3 modification. In contrast, alternative autophagy occurs independent of Atg5 expression and LC3 modification, but depends on Rab9. Although both these processes lead to bulk degradation of damaged proteins or organelles by generating autolysosomes, they seem to be activated by different stimuli, in different cell types and have different physiological roles.

research teams have shown that this mitochondrial clearance was mediated by Ulk1-dependent alternative autophagy, particularly in fetal rather than adult reticulocytes.

Q What are the implications of your findings for cell biology and beyond?

A: Our work shows the existence of an alternative protein degradation pathway that can compensate for Atg5/Atg7-dependent autophagy. More recently, we found a similar Atg5/Atg7-independent autophagy in yeast, which is activated when the movement of cargo

from the Golgi to the plasma membrane is disrupted. This pathway uses Golgi-mediated structures to enclose the material to be degraded. Just like conventional autophagy, we showed that it is phylogenetically conserved in mammals, suggesting its evolutionary importance. We have been able to identify the yeast genes required for this process and find their mammalian equivalents.

Q What future plans do you have to increase our understanding of this field?

A: We have generated mice lacking the expression of genes that control alternative autophagy. The next step is to explore the molecular mechanisms that control this process and identify their physiological relevance.



Dr. Shimizu graduated from the Faculty of Medicine at Osaka University, where he received his MD and PhD. He became Assistant Professor (1995) and Associate Professor (2000) at Osaka University. He joined TMDU as Professor of Pathological Cell Biology at Medical Research Institute in 2006.

Nature, doi: 10.1038/nature08455
Nat. Commun., doi: 10.1038/ncomms5004
EMBO J., doi: 10.15252/embj.201593191