特別講演

Physiological role and molecular mechanism of autophagy

Noboru Mizushima
Department of Biochemistry and Molecular Biology,
Graduate School and Faculty of Medicine,
The University of Tokyo

Autophagy is one of the major degradation pathways in the cell, and has multiple roles in protein metabolism, cellular quality control, and prevention of diseases such as neurodegeneration and cancer (1). In autophagy, intracellular components are sequestered by autophagosomes and then degraded upon fusion with lysosomes. Formation of the autophagosome is governed by organized functions of about 20 autophagy-related (Atg) proteins, which were originally identified in yeast. We showed that the Atg hierarchy is well conserved in other eukaryotes including mammals. We also investigated the recognition mechanism of selective autophagy substrates and found that p62 and depolarized mitochondria, and ferritin can localize to the ER-associated autophagosome formation site, independently of Atg proteins (2). These observations suggest that there is a common mechanism that recruits autophagy substrates to the autophagosome formation site, which is independent of binding to the autophagosomal membrane.

At the final step of autophagy, the autophagosome fuses with the lysosome. We recently identified the autophagosomal SNARE syntaxin 17 (Stx17) and found that it is required for the autophagosome-lysosome fusion (3). Stx17 localizes to completed autophagosomes, but not to the isolation membrane (unclosed intermediate structures); for this reason, the lysosome does not fuse with the isolation membrane.

Although these Atg proteins are highly conserved in eukaryotes, protozoa possess only a partial set of Atg proteins. The human malaria parasite *Plasmodium falciparum* possesses the complete factors belonging to the Atg8 conjugation system (Atg3, Atg4, Atg7, and Atg8). We found that PfAtg8 localizes to the apicoplast, and propose that, although *Plasmodium* parasites have lost most Atg proteins during evolution, they use the Atg8 conjugation system for the unique organelle, the apicoplast (4).

(1) Mizushima & Komatsu. Cell 147:728-41 (2011).
(2) Itakura & Mizushima. J. Cell Biol. 192: 17-27 (2011).
(3) Itakura et al. Cell 151: 1256-1269 (2012)
(4) Kitamura et al. PLoS One 7:e42977 (2012)