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Horning cell self-digestion: Autophagy wins the 2016 Nobel Prize in Physiology or Medicine

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ABSTRACT

Autophagy is an evolutionarily conserved process by which eukaryotic cells eliminate intracellular components via the lysosomal degradation process. This cell self-digestion process was first discovered and morphologically characterized in the late 1950s and early 1960s. The genetic screen studies in baker's yeast in the 1990s further identified the essential genes functioning in the autophagic process. In the past two decades, the detailed molecular process involved in the completion of autophagy was delineated. Additionally, autophagy has been implied to function in many aspects of biological processes, including maintenance of organelle integrity, protein quality control, regulation of the stress response, and immunity. In addition to maintain cell homeostasis, autophagy has recently been shown to be modulated and to participate in the pathogenesis of human diseases, such as pathogen infections, neurodegenerative diseases, and tumor development. Overall, the breakthrough in autophagy research relies on the discovery of autophagy-related genes (ATGs) using a genetic screening approach in *Saccharomyces cerevisiae*, which was established by Yoshinori Ohsumi. This year the Nobel Committee has awarded Yoshinori Ohsumi the Nobel Prize in Physiology or Medicine for his remarkable contribution to autophagy research.

The term "autophagy" is derived from the Greek words for eat ("phagy") and oneself ("auto") and was coined in the early 1960s by Christian de Duve, the 1974 Nobel Laureate in Physiology or Medicine, who discovered lysosomes and peroxisomes [1]. In response to stresses, such as nutrient deprivation, protein unfolding and aggregation, or invasion of pathogens, autophagy is activated to regulate a variety of biological pathways to counteract these adverse stimuli, thus maintaining cellular homeostasis [2,3]. The entire process of autophagy involves a stepwise membrane rearrangement process. At the initial step, the particular membraned structure, the so-called isolation membrane (IM)/phagophore, is first originated

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from various organelles, such as endoplasmic reticulum (ER) [4,5], plasma membrane [6], mitochondria [7], and Golgi apparatus [8]. Then, the IM/phagophore further elongates and encloses to form a double-membraned autophagosome. Autophagosomes sequestrate the cargo and fuse with lysosomes, forming autolysosomes in which the engulfed materials are degraded and recycled for further use by cells [2,3]. Although autophagy has been long considered a non-selective bulk degradation process, mounting evidence shows that autophagy can selectively degrade damaged organelles and infecting pathogens [2,3]. The cargo receptors of selective autophagy specifically recognize the polyubiquitinated cargo and subsequently target them to autophagic degradation via interacting with ATG8 family proteins [9,10].

Uncovering of autophagy-related genes (ATGs)

Autophagy was first characterized in the late 1950s by transmission electron microscopy observation of dense bodies that sequestrate the digestive mitochondria and ER and deliver them to be eliminated by lysosomal proteases in monkey kidney tissue and rat hepatocytes [11–14]. Later, at the 1963 Ciba Foundation symposium on lysosomes, Christian de Duve defined these sequestrating vacuoles that contain cytoplasmic components and lysosomal degradation enzymes as a cell self-lytic process and named it "autophagy" [1]. Soon afterwards, several studies noted that hormones can activate or inhibit autophagy and deprivation of nutrients; for instance, amino acids can induce autophagy [15,17–19], implying that autophagy plays a fundamental role in the catabolic process in response to external stimuli and plays a role in the recycling of nutrients [13,15–17]. In addition to mammals, the process of autophagy has also been characterized in insect and yeast cells [18–22]. An understanding of the molecules involved in the autophagy process came from research conducted in the Yoshinori Ohsumi lab, which examined the genetic screening of temperature-sensitive mutants that show defective autophagy in *Saccharomyces cerevisiae* from 1990 to 2000 [20,23,24]. Yoshinori Ohsumi's group first identified that autophagy gene 1-1 (Apg1-1) defective mutant fails to undergo the complete autophagic process due to a loss of autophagic vacuoles in yeast cells [23]. Conducting genetic studies in baker's yeast, they further identified that at least 15 Apgs are involved in the autophagy process [23]. In addition, Yoshinori Ohsumi also began to decipher the biological function of each Apg [25–30]. Similar to Ohsumi's genetic screen and findings, several autophagy-related genes were also identified and studied in yeast and other eukaryotes [31–34]. Soon after the initial discovery of Apg1-1, nearly seventy autophagy-related genes in different kinds of eukaryotes were identified and referred to as autophagy-related genes (ATGs) by the autophagy research community [35]. Now, approximately forty ATGs have been shown to be required for autophagy in yeast cells.

Autophagy research after the discovery of ATGs

After the identification of ATGs in yeast cells, Ohsumi and colleagues began to investigate the enzyme activities of these ATGs in yeast and mammals [25–30,36–46]. They delineated two ubiquitin-like conjugation cascades that are critical to autophagosome maturation: ATG5–ATG12–ATG16 and ATG8-phosphatidylethanolamine (PE) conjugation systems. The E1-like enzyme ATG7 and two E2-like enzymes ATG10 and ATG3 confer the conjugations of two ubiquitin-like modifiers, ATG12 and ATG8, into ATG5 and PE, respectively. Both of these conjugation cascades are evolutionarily conserved and necessary for the elongation and maturation of autophagosomes. Most importantly, the discovery of the conjugation of ATG8 to PE, also referred to as the lipidation of LC3, enables us to easily monitor the formation of autophagic vacuoles in cells [46]. In addition, the establishment of green fluorescent protein-tagged ATG5 transgenic mice provides a feasible tool for visualizing the autophagic process *in vivo* [47]. These remarkable works unveiling the functional roles of ATGs in the autophagic process have inspired and encouraged scientists to identify other protein complexes, including ULK and PtdIns-3 kinase complexes involved in autophagy [2,48,49].

Perspectives and implications

In the past decade, autophagy has been shown to play functional roles in the development of human diseases [2,48,49]. Hence, modulation of autophagic activity by a specific enhancer or inhibitor has therapeutic potential as a new strategy for curing human diseases. New findings and concepts regarding the regulation and function of autophagy are still growing. Additionally, several fundamental questions for autophagy, such as the origin of preautophagosomal structure and the molecular mechanism responsible for membrane regeneration of vacuoles, are still unanswered and require further investigations. Nevertheless, Yoshinori Ohsumi's tremendous contribution to autophagy research presents a hallmark for how to utilize baker's yeasts in biomedical research and has clinical implications for understanding the pathogenesis of human diseases.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

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