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Perspective

Electron-Microscope Contributions to Autophagy Research and the Nobel Prize in Physiology or Medicine 2016

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Professor Yoshinori Ohsumi received the 2016 Nobel Prize in Physiology or Medicine for his contribution to autophagy research, which was first studied using electron microscopy. To celebrate and commemorate this historical moment, I describe the role of electron microscopy in autophagy research and suggest a role for next-generation electron microscopy in this research field.

Key Words: Autophagy, Electron microscopy, Nobel Prize

The 2016 Nobel Prize in Physiology or Medicine was awarded to Professor Yoshinori Ohsumi for his contribution to autophagy research. In a recent interview, he said "I started out with a love of the microscope. Vacuoles are the only organelle visible under the light microscope, and I often observed them. My observations under the microscope were the main reason I was able to discover these hitherto unknown functions of vacuoles." (Ohsumi, 2016). Indeed, microscopic investigations have made crucial contributions to new discoveries in biological science. The resolution limit of an optical microscope, which uses visible light, is given by Abbe's diffraction limit. To overcome this limitation, electron beams were employed to take advantage of the much shorter wavelengths of these quantum particles (Ruska, 1987). Electron microscopes have revealed the detailed morphologies of intracellular organelles. The observation of mitochondria inside membrane-bounded bodies in the epithelium of a mouse kidney (Rhodin, 1954) was the first report on autophagy; the term "autophagy" was coined by de Duve (1963). As shown in Fig. 1, articles on autophagy research in the PubMed database have exponentially increased since the year 2000. This rapid growth was basically kindled by Professor Ohsumi's work on yeast (Takeshige et al., 1992), and the physiological and pathological significance of autophagy has since been addressed in several research fields. Investigations include studies of embryogenesis and cell differentiation, starvation and response to stress, oncology, bacterial and viral infections, diabetes mellitus, and neurodegenerative diseases.

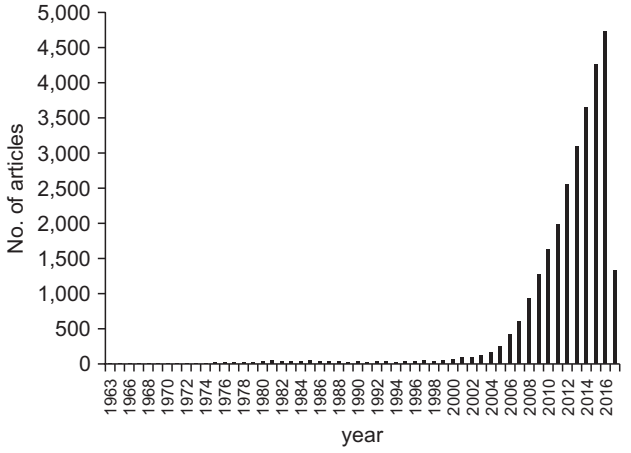

Fig. 1. Timeline showing the number of research articles on autophagy plotted as a function of the year of publication, using data from the PubMed database. An exponential increase in the number of articles has occurred since the year 2000.

From the discovery of the phenomenon of autophagy to detailed characterizations of autophagic processes, electron microscope analyses have contributed enormously. These investigations have focused on the origin of the autophagic membrane, and the formation of phagophores, autophagosomes, and autolysosomes. To understand autophagic processes, various electron-microscope research techniques have been employed. Conventional transmission electron microscopy (TEM), cytochemical and histochemical analyses, immunoelectron microscopy, electron tomography, cryoelectron microscopy, the use of freeze-fracture replicas with scanning electron microscopy, and correlative light and electron microscopy have all been applied to answer specific questions regarding autophagic processes (Eskelinen et al., 2011). For example, TEM analyses, combined with histochemistry, have been applied to understand the origin of the autophagosome; this study also suggested the de novo formation hypothesis of phagophores (Seglen, 1987). Further, the freeze-replica technique captured the fusion of an autophagosome with a lytic vacuole (Baba et al., 1995). Also, electron tomography has demonstrated the connection between phagophores and the rough endoplasmic reticulum (Yla-Anttila et al., 2009).

In addition, recently developed analysis tools for electron microscopy—such as cryotomography and focused-ion-beam/scanning electron microscopy—have been applied to elucidate the structure of the autophagosome as well as protein interactions in autophagic processes (Hurley & Nogales, 2016).

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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