【Grant-in-Aid for Scientific Research (S)】

Molecular mechanisms of autophagy against diseases and aging and the operating principle of its regulatory factors

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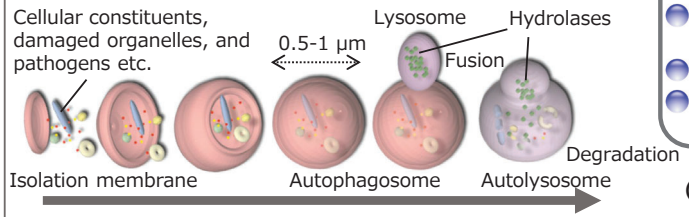
Purpose and Background of the Research

●Outline of the Research

Autophagy is a universally conserved eukaryotic system that degrades and recycles intracellular components. Autophagy begins with the appearance of a flat vesicle called the isolation membrane in the cytoplasm (Fig. 1). It stretches and curves to form a spherical autophagosome about 1 μm in diameter, encapsulating the substances and structures therein. The autophagosome then fuses with a lysosome, an organelle that degrades materials with digestive enzymes. Cells then reuse degraded materials (e.g., amino acids). Autophagy has 3 primary roles: 1) to secure nutrients during starvation, 2) to constantly replace cellular components, and 3) to separate and remove harmful substances. Autophagosome biogenesis involves unique membrane dynamics, but very few mechanisms are known, leaving many questions unanswered. Autophagy is also important for suppressing many diseases and aging, and its medical applications are eagerly awaited, but the underlying mechanisms are not well understood. In this research, we will use the key molecules and phenomena we have previously discovered as stepping stones to analyze and obtain a comprehensive understanding of the molecular mechanisms of autophagy. In particular, molecular mechanisms of non-selective and selective autophagy, membrane dynamics during autophagosome formation, and the suppression mechanism of diseases and aging by autophagy.

Figure 1. Outline of the research

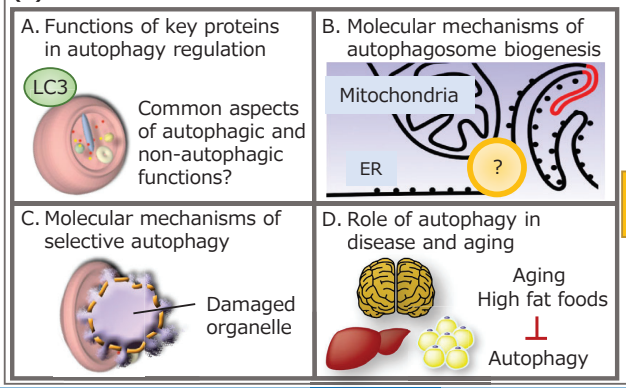
(1) Autophagy : eukaryotic intracellular degradation system



What does autophagy do?

- Secures nutrition during starvation
- Turns over cellular components
- Separates and removes harmful substances

(2) Four issues addressed in the research



(3) The aim of the research

Based on our original discoveries, we will elucidate the molecular mechanisms of autophagy and achieve its comprehensive understanding.

Autophagy suppresses various diseases and aging. Elucidating the molecular mechanisms behind this will help in medical applications of autophagy, such as the treatment and prevention of diseases, drug discovery, and the extension of a healthy life span.

●Unique characteristics of this research

The number of publications in the field of autophagy, which now numbers 10,000 per year, is dominated by phenomenological reports on the relationship with diseases and physiological roles, with only a few studies tackling the molecular mechanism head-on. This tendency can be due to the high hurdles and lack of attention, but autophagy cannot be fully understood without elucidating the molecular mechanism. Also, its medical applications that have recently attracted much interest will not be successful. Under these circumstances, this research is dedicated to unraveling the molecular mechanism of autophagy. The four issues addressed here are based on unique and important findings we obtained through a quarter century of basic research. For example, the specific function of LC3, a key molecule in autophagy regulation that we identified, is still unknown. Recently, we have found that LC3 also acts in non-autophagic events, and autophagic and non-autophagic processes likely share a common operating principle. In addition, we have discovered a specific type of autophagy that detects and sequesters harmful substances that have emerged in the cell (such as pathogenic bacteria and damaged organelles). This so-called selective autophagy has become an important topic because of its intimate association with diseases. Moreover, we have found that the expression level of an autophagy suppressing factor fluctuates with age and in a tissue-specific manner and that the resulting increase or decrease in autophagic activity is linked to pathological conditions. These are original and important discoveries, and we plan to research to expand further and work to understand autophagy from a highly original perspective.

Expected Research Achievements

●Four Research Topics

This study will address the four tasks listed in Figure 1. Task A is to elucidate the autophagic and non-autophagic actions of the autophagosome-localizing molecule LC3 and a rare autophagy suppressor factor. Elucidation of the enigmatic universal molecular mechanisms of these factors would lead to a better understanding of the regulation of intracellular membrane dynamics. In Task B, we will analyze multiple candidate factors that we have obtained through our own screening process to unravel the mysteries of autophagosome formation. The elucidation of a completely unknown mechanism of autophagosome membrane formation significantly impacts cell biology. In Theme C, we will work to elucidate the molecular mechanism of selective autophagy. Selective autophagy is important because it is strongly associated with diseases. In Issue D, we aim to elucidate the role of autophagy in disease and aging and the molecular mechanism of increase/decrease in its activity. The expression levels of an autophagy suppressor fluctuate with age and in a tissue-specific manner. The resulting increase or decrease in autophagy in disease and aging will help to understand the underlying molecular mechanisms.

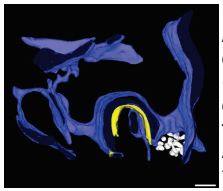


Figure 2: Autophagosomes during formation (3D image by electron tomography)
Autophagosomes form as sandwiched by the endoplasmic reticulum (cradle model).

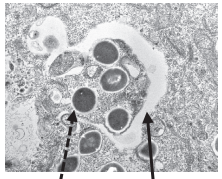


Figure 3: Example of selective autophagy
Autophagosomes selectively sequester and degrade pathogenic bacteria that have invaded the cell.

● Connection to society

Autophagy works to suppress various diseases such as neurodegenerative diseases and fatty liver, as well as aging. For this reason, applied research such as drug discovery targeting autophagy is currently active. However, understanding the molecular mechanism of autophagy through basic research is essential to realize medical applications against diseases and aging. The results obtained from this research are expected to contribute not only to academic value but also to the realization of medical applications.

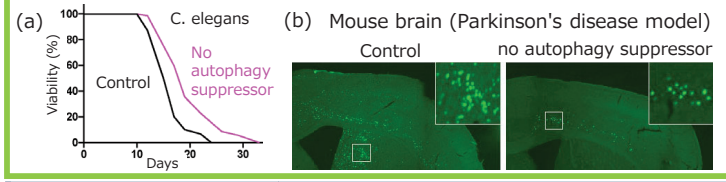


Figure 4: Inhibiting autophagy suppressor increases autophagic activity
(a) Lifespan was prolonged in C. elegans and (b) pathophysiology of age-related diseases was reduced in mice.

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