

【Grant-in-Aid for Specially Promoted Research】
Biological Sciences



Title of Project : Autophagy: Molecular mechanism and its integration into cell physiology

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Research Area : Molecular Cell Biology

Keyword : autophagy, ATG, Proteolysis, Ubiquitin like protein, Membrane dynamics, Vacuole

【Purpose and Background of the Research】

Autophagy is a major degradation system of cytoplasmic constituents and organelles in lysosome/vacuole. Since discovery of autophagy in yeast and identification of *ATG* genes essential for autophagosome formation, physiological roles of autophagy in various organisms have become one of the most hot topics in cell biology. However, there remained so many problems to solve the molecular details of autophagy. The first aim of this project is to elucidate the molecular mechanisms of membrane dynamics during autophagy based upon compilation of our works for 23 years in yeast as a model system. The second aim is to integrate the autophagy of yeast into cell metabolism, growth and differentiation under defined growth conditions.

【Research Methods】

The following different approaches will be applied to studies on the molecular mechanism and physiological significance of autophagy in yeast.

1. Analysis of molecular dynamics of Atg proteins in vivo by fluorescence microscopic imaging.
2. Biochemical analyses of interaction between Atg proteins, and regulation by phosphorylation.
3. Determination of crystal structures of all Atg proteins and their complexes.
4. Biochemical characterization of the PAS and intermediate structures during the autophagosome formation.
5. In vitro reconstitution of each reaction required for autophagosome formation
6. Metabolomic analysis during autophagy.
7. Studies on the role of autophagy in maintenance of organelle function, especially focusing mitochondrial functions.
8. Elucidation of various modes of autophagy in cell growth and differentiation.

【Expected Research Achievements and Scientific Significance】

Now it is known that most of the core machineries for the autophagosome formation are well conserved from yeast to higher eukaryotes. Since we have been working for long time yeast autophagy we have several advantages to reveal the mechanism of membrane dynamics during autophagy at a molecular level.

On the unique de novo formation of autophagosome there are many fundamental questions are remained to answer. What the origin of membrane lipids, and what are the determinants of morphogenesis of the autophagosome? We will challenge to solve these problems by combination of various research methods. These results will provide important insights into mechanism and regulation of understand the autophagy in mammals and plants.

Now using various mammalian cells, tissues and organs, it is established that autophagy is relevant to so many physiological events, such as cellular clearance, organelle quality control, and many diseases. By using well controllable yeast system, we will study the relation between autophagy and cellular metabolism, cell growth and differentiation. These systematic analyses will provide clues to understand the roles of autophagy of highly differentiated mammalian cells.

【Publications Relevant to the Project】

Nakatogawa, H. et al. *Cell*, 130, 165-178 (2007)
Okamoto, K. et al. *Dev. Cell*, 17, 87-97 (2009)

【Term of Project】 FY2011-2015

【Budget Allocation】 423,400 Thousand Yen

【Homepage Address and Other Contact Information】

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