

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

Biological Sciences (Medicine, dentistry, and pharmacy I)



Title of Project : Studies of alternative macroautophagy and its application for “Autophagic Diseases”

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Research Area : Cell Biology, Biochemistry

Keyword : Autophagy, Cell Death

【Purpose and Background of the Research】

Macroautophagy is a process that leads to the bulk degradation of subcellular constituents through the creation of autophagosomes/ autolysosomes. This process contributes to the turnover of cytoplasmic components, and has important roles in tumor suppression, prevention of neuron degeneration, and so on. Previously, it was believed that Atg5 and Atg7 are essential for induction of macroautophagy. However, recently we found that cells lacking Atg5 can still form autophagosomes/ autolysosomes, indicating that mammalian macroautophagy can occur via at least two different pathways (Fig. 1).

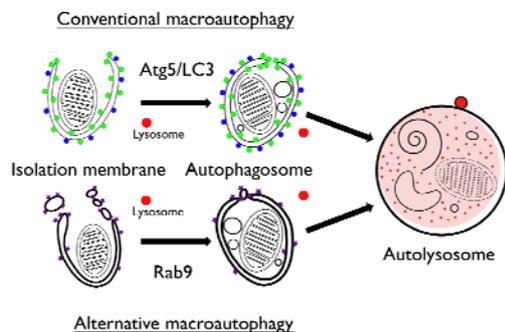


Fig.1 Mammalian cells possess two modes of macroautophagy

Therefore, for better understanding of macroautophagy, we clarify both types of macroautophagy, particularly focusing on molecular mechanisms, physiological relevance, and pathological roles.

【Research Methods】

To achieve our objectives, we plan to carry out the following studies.

(1) Molecular mechanisms of Alternative macroautophagy

First, we will classify autophagy-related molecules according to the type of macroautophagy in which they are involved. We will also identify novel molecules that are specifically involved in the alternate process of macroautophagy by using chemical biology methods.

(2) Physiological roles of macroautophagy

Gene deficient mice in which alternative macroautophagy is impaired, will be studied to elucidate the physiological roles of alternative

macroautophagy.

(3) Analysis of “Autophagy Diseases”

We will identify the autophagy-related diseases, and elucidate their pathogenesis.

(4) Drug Discovery against “Autophagy Diseases”

We will discover autophagy-inducing small compounds for applying “Autophagy Diseases”.

【Expected Research Achievements and Scientific Significance】

We will carry out the study elucidating both conventional and alternative macroautophagy that are based on our innovative achievements. We will establish a new disease concept called “autophagy diseases”, and begin to develop its treatment method.

We expect the following results. (1) Elucidation of physiological and pathological roles of macroautophagy. (2) Contribution of diagnosis and therapy for autophagy-related diseases.

【Publications Relevant to the Project】

- Nishida, Y., Arakawa, S., Fujitani, K., Yamaguchi, H., Mizuta, T., Kanaseki, T., Komatsu, M., Otsu, K., Tsujimoto, Y. and Shimizu, S. Discovery of Atg5/Atg7-independent alternative macroautophagy. **Nature** 461, 654-658 (2009)
- Shimizu, S., Kanaseki, T., Mizushima, N., Mizuta, K., Arakawa-Kobayashi, S., Thompson, C.B. and Tsujimoto, Y. Role of Bcl-2 family proteins in a non-apoptotic programmed cell death dependent on autophagy genes. **Nature Cell Biol.** 6, 1221-1228 (2004)

【Term of Project】 FY2010-2014

【Budget Allocation】 167, 200 Thousand Yen

【Homepage Address and Other Contact Information】

<http://www.tmd.ac.jp/mri/pcb/index.html>