【Grant-in-Aid for Transformative Research Areas（B）】

Section III

Title of Project： Post-lysosome: Understanding of higher-order biological processes initiated by the site of degradation

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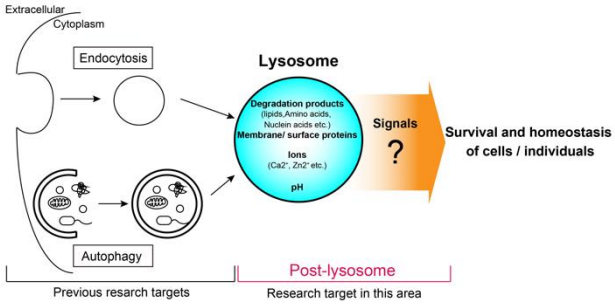
【Purpose of the Research Project】

Lysosomes are membrane-enclosed acidic organelles that contain arrays of enzymes capable of breaking down several intracellular and extracellular materials. Extracellular materials and plasma membrane components are delivered to lysosomes via endocytic pathway, whereas cytosolic components and organelles are delivered to lysosomes by autophagy. Traditionally, studies of these degradation pathways have focused on elucidating the mechanism of transport to lysosomes, and in fact their understanding has dramatically increased in recent decades (Fig. 1). However, lysosomes function as digestive system may be only a part of their original function. In fact, recent successive discoveries have revealed that lysosomal degradation products and various lysosomal components play a role in maintaining cell / individual homeostasis by actively participating in signal transduction within cells and between cells / tissues (Fig. 1). In other words, it is thought that organisms incorporate the process after transporting substances to lysosomes, 'post-lysosomes', as part of the survival strategy of cells and individuals, but actual signals working in post-lysosomes and their precise functions remain elusive. In this research project, we aim to understand the regulation of lifespan and aging as one of higher-order biological processes through the elucidation of signals that work in post-lysosomes. Our research project will fundamentally change the existing concept that lysosomes are merely the end points of degradation products and will lead to the creation of a new research area, "post-lysosomal biology," which focuses on the biological processes mediated by signals originating from lysosomes.

Figure 1 Research target in this area



【Content of the Research Project】

In this study, we have organized four groups consisting of young researchers in the field of autophagy and lysosomes, aging research and lipid biology, and will conduct individual planned research and collaborative research using nematodes, flies, turquoise killifish and cultured mammalian cells to uncover the core mechanism regulating lifespan and aging through the elucidation of signals that work in post-lysosomes. Using several models modulating lysosomal functions, novel post-lysosomal signals will be identified by a genetic approach (A01 Osaka University, Nakamura) and multi-omics analysis (C03 Tokyo Institute of Technology, Fujita). Considering lipids as one of the promising candidates for post-lysosomal signals, we will prioritize lipid analysis by combining the development of new lipid probes and lipidomics analysis (B02 The University of Tokyo, Nishimura). Since understanding of inter-tissue communications is particularly important in individual aging, we will identify the major tissue responsible for the post-lysosomal signals mediating these communications (C03 Tokyo Institute of Technology, Fujita). Lifespan and aging are strongly influenced by external factors such as environmental stimuli in addition to internal factors regulated by genes. Focusing on the gut microbiota, which is closely related to longevity and aging and is located at the interface between internal and external factors, we will clarify the crosstalk with post-lysosomal signals (D04 Osaka University, Abe). The evolutionally conserved functions of the identified novel post-lysosomal signals will be examined by collaborative works in four groups using nematodes, flies, turquoise killifish and cultured mammalian cells.

【Expected Research Achievements and Scientific Significance】

Extending healthspan is an urgent task in developed countries facing a super-aging society. In order to establish the method to delay aging in humans, understanding the basic molecular mechanism controlling aging and lifespan is essential. The elucidation of the post-lysosomal signals and their evolutionally conserved functions can potentially uncover this big mystery and will be the basis for establishing a new method contributing to healthy longevity. Furthermore, since signal transduction originating from lysosomes is thought to be closely linked to many biological processes, not limited to aging and lifespan control, the promotion of post-lysosome research will contribute to the understanding of almost all fields in life sciences.

【Key Words】

Post-lysosome biology:　A discipline dealing with biological phenomena mediated by signals originating from lysosomal degradation products and various components.

【Term of Project】

FY2021-2023

【Budget Allocation】

104,800 Thousand Yen

【Homepage Address and Other Contact Information】

https://post-lysosome.jp/