【Grant-in-Aid for Specially Promoted Research】

Research on intracellular degradation focusing on membranous structures

Principal Investigator	The University of Tokyo, Graduate School of Medicine, Professor MIZUSHIMA Noboru　　Researcher Number:10353434
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Purpose and Background of the Research

●Outline of the Research

Organelles are compartmentalized by membranes. Intracellular membranes are estimated to occupy 20–50 times the area of the plasma membrane. Large amounts of organelles are continuously synthesized and degraded. Organelles are thought to be degraded mainly by autophagy; however, because it is difficult to detect membranes, the dynamics of membranes that are involved in degradation have not been systematically analyzed (Fig. 1). In addition, we recently discovered a novel organelle degradation system that involves cytosolic lipases, expanding the diversity of membrane-degradation mechanisms beyond autophagy (Fig. 1). Moreover, membrane degradation can be selective. Some membranes are degraded by lysosomal enzymes, whereas other membranes are not degraded (Fig. 2). However, the mechanism of such selective membrane degradation is not known. In this research project, we aim to elucidate the dynamics, mechanisms, and physiological significance of the degradation of intracellular membranous structures.

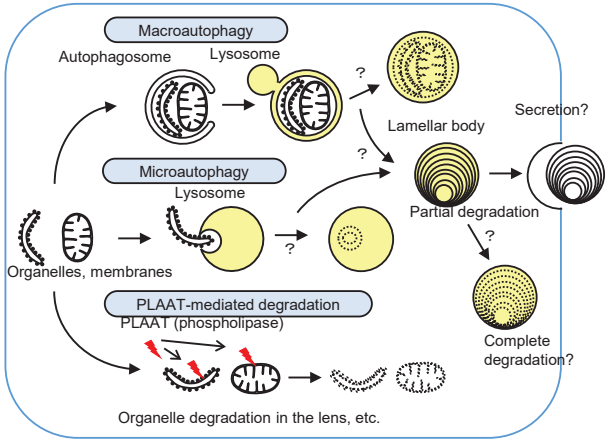

Figure 1. . Degradation of intracellular membranes

●Aim 1. Analysis of organelle degradation by autophagy

The degradation of organelle-derived membranes transported into lysosomes during autophagy has not been investigated systematically. Lamellar bodies containing undigested membranes are often observed in many types of cells. However, the fate and dynamics of lamellar bodies are largely unknown, except in type 2 alveolar epithelial cells. Thus, we will systematically analyze the degradation process of intracellular membranous structures. The mechanisms of selective recognition of organelles such as mitochondria and the ER and the physiological significance of organelle degradation will also be investigated.

●Aim 2. The mechanism and roles of organellar degradation by PLAAT family lipases

We previously reported that organelle degradation in the lens is independent of autophagy and is mediated by PLAAT lipases. We will work to reveal the mechanisms of PLAAT recruitment and insertion into membranes. We will also attempt to elucidate the physiological significance of the PLAAT-mediated organelle degradation in non-lens tissues.

●Aim 3. Selective membrane degradation

Intracellular membrane degradation can be selective. For example, the inner membrane (red) but not outer membrane (bule) is degraded after fusion with lysosomes (Fig. 2). In the case of microautophagy and multivesicular bodies (late endosomes), only the membranes of intraluminal vesicles are degraded. We will work to reveal the mechanism underlying the selective degradation.

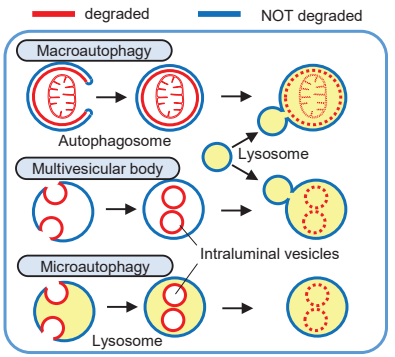

Figure 2. Selective membrane degradation by the lysosome

Expected Research Achievements

●Establishment of new tools for intracellular membrane degradation research

To investigate intracellular membrane dynamics and membrane degradation, we will establish methods to label membrane lipids and to detect membrane degradation in a highly sensitive and specific manner.

●Significance of this study in intracellular degradation research

Given that intracellular compartmentalization is common in the membranes of eukaryotes, understanding membrane degradation is essential for biology. If the dynamics, mechanisms, and significance of the degradation of intracellular organelles and membranes is comprehensively clarified, it will open up a new research field (Figures 3 and 4). Although much progress has been made in understanding the mechanism of autophagy over the past 20 years, most of the progress has been focused on the autophagosome formation step. Research on the later steps, including membrane degradation, is necessary for a comprehensive understanding of autophagy.

●Expected impact on aging and disease research fields

This study has the potential to develop into a new area of intracellular quality control research. Membrane degradation might be particularly important in non-dividing cells such as neurons. Indeed, the accumulation of membrane-like structures in lysosomes is observed in many lysosomal storage diseases and likely occurs in people of advanced age. Furthermore, degradation of the membranes of mitochondria and lysosomes is related to autoimmune diseases and gouty nephropathy, respectively. This study will be useful in understanding these diseases.

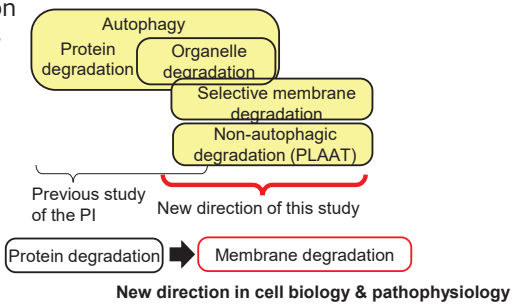

Figure 3. Direction of this study

Homepage Address, etc.	Lab web paper: https://molbiolut.jp/en/ Publon: https://publons.com/wos-op/researcher/1353325/noboru-mizushima/