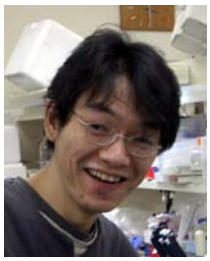

Title of Project：Pathophysiological roles of selective autophagy

Masaaki Komatsu
(Tokyo Metropolitan Organization for Medical Research, Tokyo Metropolitan Institute of Medical Science, Project Sub-Leader)

Research Area：Pathophysiology
Keyword：Autophagy, p62, Nbr1, Aggregate, Ubiquitin

【Purpose and Background of the Research】

Autophagy is a highly conserved bulk protein degradation pathway in eukaryotes. Emerging evidence emphasizes the importance of autophagy in various biological and pathological processes, such as cellular remodelling, tumorigenesis and developmental programmes. Recent evidence indicates that autophagy serves two physiological purposes. The first is to supply amino acids for cell survival under poor-environmental conditions, which is universally known as 'adaptive autophagy'. The second is to degrade proteins in the cell through continuous operation at a low level irrespective of nutritional stress, known as 'basal or constitutive autophagy'. In the latter pathway, autophagy is responsible for the turnover of long-lived proteins, disposal of excess or damaged organelles, and clearance of aggregate-prone proteins.

【Research Methods】

Our genetic studies using mice have highlighted the importance of constitutive autophagy in non-dividing cells, such as hepatocytes and neurons, in which loss of autophagy results in severe liver injury and neurodegeneration, respectively. Unexpected findings in these studies were that loss-of-autophagy causes cytoplasmic accumulation of ubiquitin-positive proteinaceous aggregates, together with hepatocytic and neuronal death without expression of proteins with disease-associated mutations. However, the underlying mechanism of aggregate formation in the aforementioned diseases has been largely unknown. Recently, we found that selective turnover of a ubiquitin-binding protein, p62 via autophagy regulates the protein aggregate formation and liver homeostasis. Indeed, loss of p62 in autophagy-deficient mice leads to mitigation of severe liver injury observed in autophagy-deficient mice. We aim to clarify the physiological roles of constitutive autophagy, and its selectivity for target proteins. Using mouse genetic studies for autophagy and its selective substrates, we clarify pathophysiological roles of the selective substrates.

【Expected Research Achievements and Scientific Significance】

An understanding of the cellular fluctuations caused by increased amounts of autophagy-selective substrayes and/or failure in autophagy would provide us with important clues towards a new therapeutic approach for treating various human diseases.

【Publications Relevant to the Project】

1. Komatsu M et al., Loss of autophagy in the central nervous system causes neurodegeneration. ***Nature***, 441, 880-884 (2006)
2. Komatsu M et al., Homeostatic levels of p62 control cytoplasmic inclusion body formation in autophagy-deficient mice. ***Cell***, 131, 1149-63 (2007)

【Term of Project】 FY2009-2013

【Budget Allocation】 83,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.rinshoken.or.jp/MO/index.html