【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project：
In-depth Analysis of Proteasome-Mediated Regulatory Proteolysis

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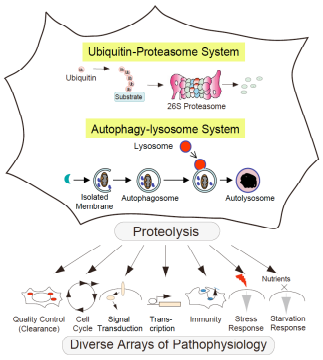
Research Area：Cell biology

Keyword： Protein degradation

【Purpose and Background of the Research】

Protein degradation plays an important role in the control of a diverse array of basic cellular activities by rapidly and unidirectionally catalyzing biological reactions. The degradation machinery in eukaryotic cells consists of two main systems; one mediated by the proteasome and the other by autophagy (Figure). The proteasome, in collaboration with the ubiquitin system used for choice of target proteins, selectively degrades short-lived regulatory proteins as well as abnormal proteins that must be eliminated from the cells. In contrast, the lysosome-linked autophagy (self-eating) is a bulk protein degradation system designed to engulf cytoplasmic constituents in a non-selective fashion, and plays a prominent role in starvation response and quality control of proteins and organelles in cells. Over the past 25 years, our research work focused on elucidating the structure and molecular/physiological functions of the proteasome. Notwithstanding the above achievements, there are still many unanswered yet important questions in this field.



【Research Methods】

(a)Many uncharacterized PIPs (proteasome interacting proteins), and factors related to ubiquitin and autophagy are identified by using the LC-MS/MS system. (b) Novel factors involved in transcription, assembly, activity, and localization of the proteasome are designed to identify by genome-wide RNAi screening. (c) Genetic studies in mice are conducted to investigate the *in vivo* functions of apparently important factors.

【Expected Research Achievements and Scientific Significance】

First, we will continue to gain further insights into the molecular mechanisms involved in the structures, functions, and regulations of proteasomes. In addition, the aim of our new studies will be to identify the unique roles of the ubiquitin and autophagy systems. The following section describes the main hypotheses and goals of the proposed project in a brief format.

Proteasome Study: The proteasome is now a key word for understanding life science. We propose the following framework for a comprehensive study of the proteasomes. (a) Studies to determine the molecular mechanisms underlying the 26S proteasome assembly. (b) Studies to characterize the *in vivo* roles of chaperone-dependent proteasome assembly. (c) Studies on the immunoproteasome and thymoproteasome designed to determine the roles and underlying mechanisms of the immune regulation.

Ubiquitin Study: Analyses of Parkin (responsible gene of familial early-onset Parkinson's disease encoding ubiquitin ligase), Fbs family (sugar-recognizing ubiquitin ligases), Rfu1 (ubiquitin homeostasis factor), and Ufm1 (ubiquitin-fold modifier 1) are proposed.

Autophagy Study: Our previous studies have shown the homeostatic roles of constitutive autophagy in selective clearance of unfavorable proteins in non-dividing cells, such as hepatocytes and neurons. Based on these recent results, we plan to investigate how selective autophagy operates in these cells and how disordered autophagy is involved in pathogenic events. Considering the above-described issues, the anticipated results shall yield basic information on the mode of action and pathophysiological mechanisms of intracellular proteolysis, which contribute to the surveillance and maintenance of human health in general.

【Publications Relevant to the Project】

Murata, S., et al., Regulation of $CD8^+$ T cell development by thymus-specific proteasomes. Science 316, 1349-1353 (2007)

Murata, S., Yashiroda, H., and Tanaka, K. Molecular mechanisms of proteasome assembly. Nature Rev Mol Cell Biol 10, 104-115 (2009)

【Term of Project】 FY2009-2013

【Budget Allocation】 621, 000 Thousand Yen

【Homepage Address and Other Contact Information】 http://www.rinshoken.or.jp