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

Title of Project： Dynamics and function of the proteasome

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Research Area： Biological science, Functional biochemistry
Keyword： Proteolysis

【Purpose and Background of the Research】

The proteasome is the major protease in eukaryotic cells. By catalyzing degradation of ubiquitinated proteins, it plays essential roles in various cellular events including cell cycle, transcription, signal transduction, and protein quality control.

Recent studies have revealed a connection between proteasome activity and human diseases and physiologies such as cancer, metabolic diseases, neurodegenerative diseases, maintenance of ES/iPS cell pluripotency, and senescence. However, mechanisms by which the expression and activity of the proteasome is regulated are largely unresolved.

In this research project, we will study the mechanisms of proteasome regulation and mechanisms whereby aberrant proteasome function leads to various human disease states.

【Research Methods】

To achieve our goal, we will carry out analyses in the following areas.

(1) Molecular assembly of the proteasome:
We will elucidate the molecular mechanism by which the elaborate structure of the proteasome is accurately assembled from 33 different subunits (66 subunits in total).

(2) Transcriptional regulation of the proteasome:
Stress-responsive transcription factors, Nrf1 and Nrf2, have been shown to promote concerted upregulation of proteasome subunit genes when the proteasome is compromised. However, molecules involved in the basal expression of the proteasome subunits remain unknown. We will address this issue by identifying the responsible factors.

(3) Dynamics of the proteasome:
The proteasome changes its subcellular localization depending on its cellular environment; it accumulates in the nucleus in tumor cells, while dispersing through both the cytosol and the nucleus in normal cells. We will clarify the regulatory mechanism and the physiological significance of the intracellular dynamics of the proteasome.

(4) Pathophysiology and the proteasome:
Mice in which the function of the proteasome is impaired show various pathologies such as early senescence, mitochondrial morphological defect, and metabolic abnormality. We will resolve molecular mechanisms that induce these pathologies when the proteasome is impaired.

【Expected Research Achievements and Scientific Significance】

Most tumor cells express higher levels of proteasomes than normal cells, which is one of the reasons why proteasome inhibitors are effective for clinical use against certain kinds of malignant tumors. In contrast, proteasome activity decreases as an organism ages. The fact that flies and worms with higher proteasome activity live longer than normal ones suggests that attenuation of proteasome activity is the major cause of age-related diseases. Thus, our research will not only contribute to the understanding of proteasome regulation but also be of vital importance to the development of new drugs and treatments against diseases related to the dysregulation of proteasome activity.

【Publications Relevant to the Project】

- Sasaki K, Hamazaki J, Koike M, Hirano Y, Komatsu M, Uchiyama Y, Tanaka K, Murata S. PAC1 gene knockout reveals an essential role of chaperone-mediated 20S proteasome biogenesis and latent 20S proteasomes in cellular homeostasis. Mol Cell Biol 20, 3864-3874, 2010.
- Kaneko T, Hamazaki J, Iemura S, Sasaki K, Furuyama K, Natsume T, Tanaka K, Murata S. Assembly pathway of the mammalian proteasome base subcomplex is mediated by multiple specific chaperones. Cell 137, 914-925, 2009.

【Term of Project】 FY2013-2017

【Budget Allocation】 133, 200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.f.u-tokyo.ac.jp/~tanpaku/