【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

# Title of Project : The Proteasome: Mechanistic Actions and In-depth Physiopathological Analyses

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Research Project Number : 26000014　Researcher Number : 10108871
Research Area : Cell biology
Keyword : Protein degradation

## 【Purpose and Background of the Research】

All proteins, major constituents and functional elements of biological activity in cells, are heterogeneously turning over with distinct lifespans. The proteasome, a central proteolysis apparatus in eukaryotes, plays an essential role for a diverse array of vital phenomena by catalyzing biological reactions rapidly, orderly, and unidirectionally. Over the past quarter of a century since its discovery, our research work has comprehensively elucidated the structures and functions of proteasomes, and our group has been a pioneer in this field and the worldwide authority. The goal of the present study is to elucidate the fundamental mechanisms of the proteasome and its integration into physiopathology. On another front, we have pursued studies on ubiquitin and autophagy collaborating with the proteasome, whose abnormality causes intractable diseases such as neurodegenerative disorders and cancers that have been increasing, especially in today's aging society. We are confident that the proposed projects will contribute not only to clarification of the cause of the aforementioned diseases but also to exploring new and exciting areas in life science.

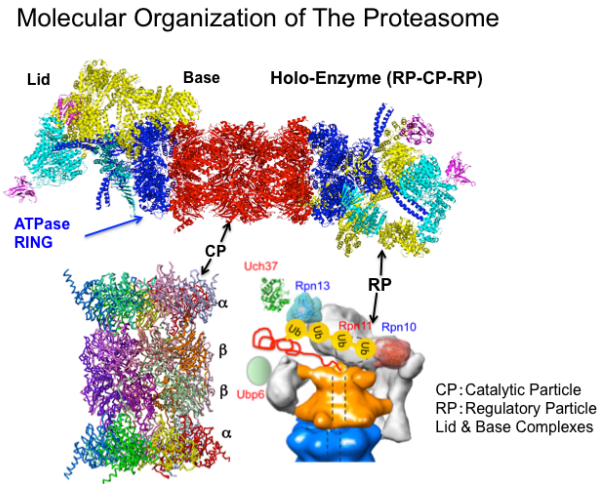
## 【Research Methods】

We use many cutting-edge technologies in life science, such as biochemistry, cell biology, molecular biology, structural biology, genetics, and immunology.

## 【Expected Research Achievements and Scientific Significance】

Subject 1: Mechanistic actions and assembling mechanisms: We showed that the proteasome is a large multisubunit complex that consists of a CP and two RPs (Fig). To date, all efforts to define the atomic structures of the whole proteasome have failed, presumably because of their fragile nature. In this proposal, we will use various physicochemical technologies to analyze a dynamic state of the proteasome in a spatiotemporal fashion. During the past decade, we have revealed the molecular mechanisms underling proteasome assembly by discovery of about 10 proteasome-dedicated assembling chaperones. We will conduct genetic and structural analyses of these chaperone molecules.

Subject 2: Unraveling the mechanisms of neurodegenerative diseases: The two genes, *PINK1* and *Parkin*, link to the familial forms of early-onset Parkinson's disease (PD). We have revealed that mitochondrial quality control is a key factor in PD pathogenesis. However, the exact mechanism of their functional interplay remains an enigma. Accordingly, we will investigate how PINK1 and Parkin operate under mitochondrial stresses to maintain mitochondrial integrity.




Subject 3: Establishment of basic principles of immunology: Recently, we proposed a key role of the thymoproteasome in the development of the MHC class I-restricted $CD8^+$ T cell repertoire during thymic positive selection. However, the exact role of the thymoproteasome is still unknown. Accordingly, we aim to gain definitive evidence for our 'thymoproteasome-mediated positive selection' hypothesis and consequently change some of the fundamental principles of immunology.

## 【Publications Relevant to the Project】

・Koyano, F., Okatsu, K. et al., Ubiquitin is phosphorylated by PINK1 to activate parkin. Nature 510,162-166 (2014)
・Murata, S., Sasaki, K. et al., Regulation of $CD8^+$ T cell development by thymus-specific proteasomes. Science 316, 1349-1353 (2007)

## 【Term of Project】

FY2014-2018

## 【Budget Allocation】

312,800 Thousand Yen

## 【Homepage Address and Other Contact Information】

http://www.igakuken.or.jp/pro-meta/