【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project: Comprehensive and expansive research of the universal metabolic regulation mechanisms for healthspan

Takashi Kadowaki
(The University of Tokyo and The University of Tokyo Hospital, Professor)

Research Project Number : 26000012　Researcher Number : 30185889
Research Area: Metabolism
Keywords: diabetes, signal transduction, biological molecular medicine, healthy longevity, adiponectin

【Purpose and Background of the Research】

Evolution of all organisms on earth reflects a history of their attempts to adapt to famine or malnutrition which determined the life span of each organism including humans. In fact, until recently, malnutrition, compromised immunity associated with malnutrition, and infections, had been the major causes of human deaths. However, from the latter half of the 20th century, humankind has entered an era of unprecedented hypernutrition, which is triggering diseases that have come to be termed "lifestyle-related diseases" and reducing the life spans of affected individuals. To fundamentally solve all the problems brought about by these drastic changes in nutrition and the environment that have occurred in a short time, it is essential to gain a panoramic view of universal life phenomena occurring in organisms in a variety of nutritional and environmental conditions, and gain an understanding of the mechanisms of their disruption. This research aims at elucidating universal metabolic pathways for healthy longevity, and establishing the methods for its realization.

【Research Methods】

The applicants aim to identify biologic responses as well as mechanisms of their regulation in various types and degrees of nutritional environments by utilizing the metabolome, epigenetic and transcriptome analytical methods. Using the information gained, the applicants attempt to gain a panoramic view of the biological responses, which are determined by nutritional and other environmental conditions, and expressed as aging and lifespan in individual living organisms, as a consequence of each organ's different responses and coordination among the organs. In this regard, the applicants recently clarified that the anti-diabetic hormone adiponectin(Ad) /AdipoR signals are newly implicated in determining lifespan, and succeeded in obtaining Ad/AdipoR signal-activating small-molecular compound: AdipoRon (Fig.1). Thus, the applicants propose to identify novel universal metabolic pathways involved in healthy longevity, other than Ad or known longevity-associated genes.

Ultimately, the aims are to identify the universal metabolic pathways related to healthy longevity, and build scientific evidences to allow the advancement to the stage of clinical research of AdipoR-activating drug as a healthy longevity medication.

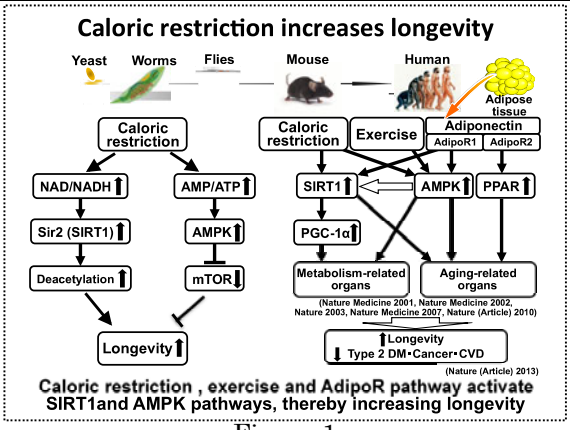

Figure 1

【Expected Research Achievements and Scientific Significance】

This proposed research aimed at clarifying the universal mechanisms of metabolic regulation should allow the applicants to provide evidence-based answers to the questions, "What is an optimal diet?" and "What steps need to be taken to achieve health longevity?" Acquisition of evidence for optimizing AdipoR signal-activating small-molecular compounds for human applications will help realize clinical research and drug discovery, and contribute greatly to realizing the treatment of diabetes and lifestyle-related diseases, and ultimately, to making healthy longevity a reality. The applicants feel that this is a highly significant, all-encompassing research endeavor which leads to the conquest of lifestyle-related diseases and the creation of a lively aging society, as well as to the realization of pre-emptive medicine.

【Publications Relevant to the Project】

- Okada-Iwabu M, Yamauchi T, Iwabu M, (13 authors), and Kadowaki T. A small-molecule AdipoR agonist for type 2 diabetes and short life in obesity. *Nature* 503, 493-499 (2013).
- Iwabu M, Yamauchi T, Okada-Iwabu M, (22 authors), and Kadowaki T. Adiponectin and AdipoR1 regulate PGC-1 alpha and mitochondria by Ca^{2+} and AMPK/SIRT1. *Nature* 464, 1313-1319 (2010).

【Term of Project】 FY2014-2018

【Budget Allocation】 394,800 Thousand Yen

【Homepage Address and Other Contact Information】 http://dm301k.umin.jp

【Grant-in-Aid for Specially Promoted Research】

Biological Sciences

Title of Project : Study of design principle underlying seasonal time measurement and its application

Takashi Yoshimura
(Nagoya University, Graduate School of Bioagricultural Sciences, Professor)

Research Project Number : 26000013 Researcher Number : 40291413
Research Area : Agricultural sciences
Keyword : Physiology

【Purpose and Background of the Research】

Organisms measure day length to adapt their lives to the seasonal alterations of the earth, and its mechanism is one of the great mysteries in biology today. Although this phenomenon currently attracts tremendous general interest, its mechanism remains unknown in any living organism.

In the previous study, we have uncovered a comprehensive picture of the vertebrate photoperiodic signal transduction pathway (Figure 1). However, it remains unknown just how the biological clock measures day length. Additionally, it is not known how animals adapt to seasonal changes in temperature. In this project, we aim to clarify the design principle underlying seasonal time measurement in vertebrates.

We also aim to design and synthesize transformative bio-molecules that act as substitutes for key molecules to improve animal production and human health by taking full advantage of cutting-edge chemical synthesis expertise.

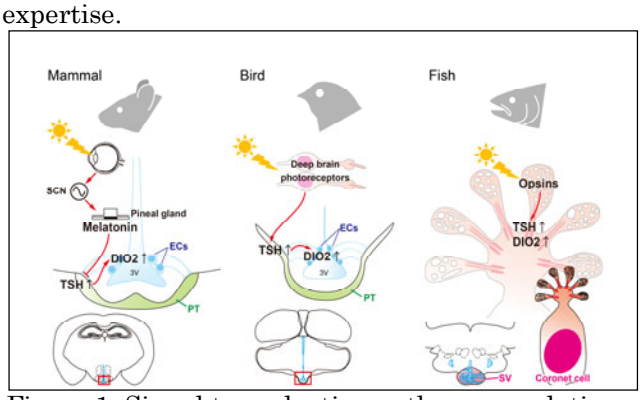

Figure 1. Signal transduction pathway regulating vertebrate seasonal reproduction.

【Research Methods】

Uniqueness of our research lies in the use of various organisms. We will uncover the design principle of seasonal time measurement using mouse, quail, and medaka fish by various methods including transcriptome analysis and genome wide association study. In addition, we will develop transformative bio-molecules by cutting-edge chemical synthesis.

【Expected Research Achievements and Scientific Significance】

Most animals give birth in spring to ensure survival of the offspring, when a moderate climate and abundant food are available. Although seasonal breeding is a clever strategy allowing animals to survive in a changing environment, it is a rate-limiting factor in the aquaculture, poultry, and livestock industries. Thus, understanding of its mechanism is highly relevant to animal production. According to ethical and safety concerns, chemicals that specifically control seasonal reproduction are required. Development of "transformative bio-molecules" represents a powerful strategy and it would cause a paradigm shift in animal production. Seasonal affective disorder and other seasonally related health problems are also reported in human. Thus, this project also has great impact on human reproductive health and mood disorders.

【Publications Relevant to the Project】

・Nakao N, et al., Thyrotrophin in the pars tuberalis triggers photoperiodic response. ***Nature*** 452, 317-322 (2008)
・Nakane Y, et al., A mammalian neural tissue opsin (Opsin 5) is a deep brain photoreceptor in birds. ***Proc Natl Acad Sci USA*** 107, 15264-15268 (2010)
・Nakane Y, et al., The saccus vasculosus of fish is a sensor of seasonal changes in day length. ***Nature Communications*** 4, 2108 (2013)

【Term of Project】 FY2014-2018

【Budget Allocation】 294, 800 Thousand Yen

【Homepage Address and Other Contact Information】

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

Keiji Tanaka
(Tokyo Metropolitan Institute of Medical Science, Director General)

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.

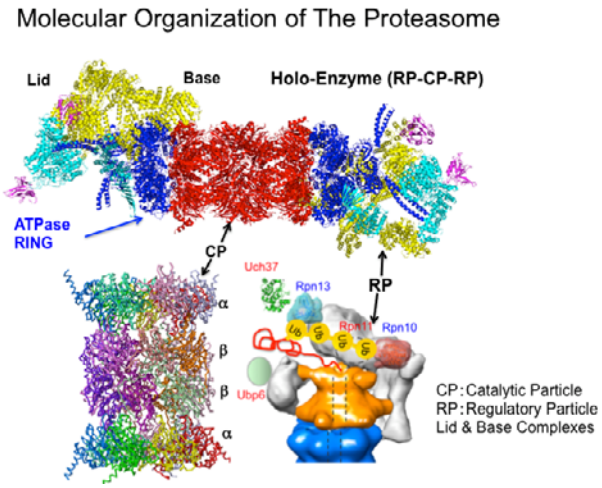
【Research Methods】

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/