

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

Biological Sciences (Medicine, dentistry, and pharmacy)



Title of Project : Comprehensive research of the universal metabolic regulation mechanisms for health-span

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Research Area : metabolomics

Keyword : healthy longevity, adiponectin, AdipoR

【Purpose and Background of the Research】

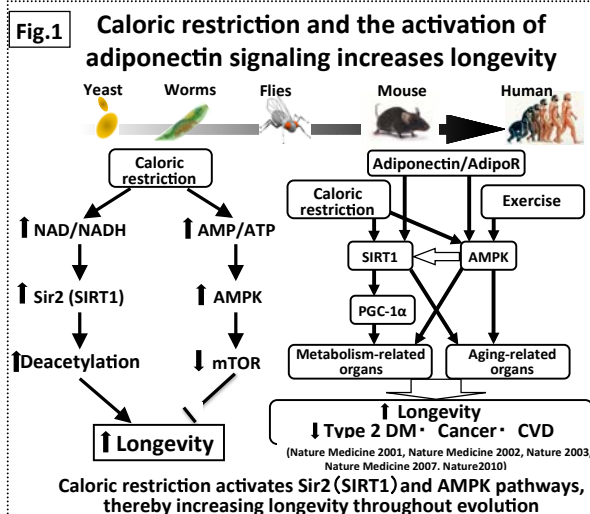
The evolution of all organisms on earth reflects a history of their attempts to adapt to famine or malnutrition, which determined the life span of each organism including humans. In fact, malnutrition or compromised immunity associated with malnutrition was among the major causes of mortality. However, from the latter half of the 20th century, humankind has entered an era of unprecedented hypernutrition, which led to the onset of diseases that have come to be termed “lifestyle-related diseases” and are responsible for shortened life spans in affected individuals. To provide definitive solutions to all such issues associated with these drastic changes in nutrition as well as in the environment that have occurred in a short time, it is essential to gain a panoramic view of life phenomena occurring in organisms in a variety of nutritional and environmental conditions, get to the core of these phenomena, and gain an understanding of the mechanisms of their disruption.

【Research Methods】

The applicants propose to clarify biologic responses (nutritional signals) as well as mechanisms of their regulation in varying nutritional environments by drawing on the metabolome, epigenetic and transcriptome analytical methods at our disposal. Based on information gained, the applicants intend to gain a panoramic view of the biological responses expressed as aging and lifespan in living organisms as a consequence of different biological responses and coordination among their organs (longevity signals). In this regard, the applicants recently clarified that the anti-diabetic hormone adiponectin/AdipoR signals are new signals deeply implicated in determining lifespan and succeeded in obtaining adiponectin/AdipoR signal-activating agents (Fig.1). Thus, the applicants propose to perform analyses of organ-specific biologic responses in varying environments including nutrition, by using various animals whose AdipoR is genetically engineered to block or enhance their adiponectin/AdipoR signaling and the above-mentioned AdipoR signal-activating small-molecular compound, thereby identify novel universal metabolic pathways involved in healthy longevity in addition to adiponectin or the longevity-associated genes already reported.

【Expected Research Achievements and Scientific Significance】

Through our proposed research aimed at clarifying



the universal mechanisms of metabolic regulation in place, the applicants feel we should be able to provide evidence-based answers to such questions as “What is an optimal diet?”, “How do we go about achieving health longevity?”. In more scientific terms, the applicants propose to carve out “comprehensive life science” as an interdisciplinary area integrating areas as diverse as biochemistry, molecular biology, cell biology, structural biology, metabolism and diabetology, which the applicants feel will have great impact as an 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】

- Yamauchi T, (24 authors) & Kadowaki T. Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 423, 762-769 (2003)
- Iwabu M, Yamauchi T, Okada-Iwabu M, (22 authors) & Kadowaki T. Adiponectin and AdipoR1 regulate PGC-1α and mitochondria by Ca²⁺ and AMPK/SIRT1. *Nature* 464, 1313-1319 (2010)
- Yamauchi T, Kadowaki T. Adiponectin receptor as a key player in healthy longevity and obesity-related diseases. *Cell Metab.* 17, 185-196 (2013)

【Term of Project】 FY2013-2017

【Budget Allocation】 177, 200 Thousand Yen

【Homepage Address and Other Contact Information】

<http://dm301k.umin.jp>