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

Title of Project : Signal Transduction Networks Regulating Life-span and Development

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Research Project Number : 26221101 Researcher Number : 60143369
Research Area : Functional biochemistry
Keyword : Cell signal transduction

【Purpose and Background of the Research】

The nematode Caenorhabditis elegans (C. elegans) is a powerful model organism for studying animal life-span, because it is amenable to molecular genetic approaches, and has a short life-span. We have previously found that intermittent fasting, a dietary regimen with repeated cycles of fasting and ad libitum feeding, extends C. elegans life-span more efficiently than calorie restriction, another dietary regimen in which food intake is chronically restricted. Moreover, we have uncovered fasting-driven intracellular signaling pathways, transcription factors, and downstream longevity-related genes (Honjoh et al., Nature 457, 726-730. 2009; Uno et al., Cell Rep. 3, 79-91. 2013). The first purpose of this research project is to extend our above findings by further elucidating signal transduction networks regulating fasting (or other external stress)-induced longevity, especially focusing on related epigenetic pathways and small chemicals.

The second purpose is to elucidate signal transduction networks regulating developmental processes. We previously found that control of the duration of ERK MAP kinase activity is essential for dorsoventral patterning in Xenopus embryos (Hanafusa et al., Nature Cell Biol. 11, 106-109, 2009). We also found that the kinase SGK1, whose expression is shown to be induced by sustained ERK activation, promotes ectodermal cell survival in Xenopus embryos through a non-cell-autonomous signaling pathway (Endo et al., Sci. Signal. 4, ra2, 2011). In this research project, we will examine developmental roles of ERK signal transduction networks, especially focusing on ERK-regulated ectodermal genes. Also, we will examine developmental roles of other MAP kinases and related signaling pathways. Moreover, we will search external environment factors (such as nutrients and mechanical stress) regulating development and regeneration, and identify related intracellular signaling pathways as well as related epigenetic pathways.

【Research Methods】

We use C. elegans and Xenopus as model organisms to examine signal transduction networks regulating life-span and development. We will carry out gene expression analysis by microarray and next-generation sequencing, promoter analysis using bioinformatics (Sunadome et al., Dev. Cell 20, 192-205. 2011; Uno et al., Cell Rep. 3, 79-91. 2013), systematic RNA interference screening, systematic screening of mutants, knockdown experiments using antisense morpholino oligonucleotides, and chemical biology approaches.

【Expected Research Achievements and Scientific Significance】

Our research project will uncover novel signal transduction networks and related epigenetic pathways regulating life-span and development, as well as their interrelationships with external environment factors including nutrients and stresses. The future goal is to promote comprehensive understanding of molecular mechanisms regulating life-span and development.

【Publications Relevant to the Project】

Uno, M., Honjoh, S., Matsuda, M., Hoshikawa, H., Kishimoto, S., Yamamoto, T., Ebisuya, M., Yamamoto, T., Matsumoto, K., and Nishida, E. A fasting-responsive signaling pathway that extends life span in C. elegans. Cell Rep. 3, 79-91 (2013).
Endo, T., Kusakabe, M., Sunadome, K., Yamamoto, T., and Nishida, E. The kinase SGK1 in the endoderm and mesoderm promotes ectodermal survival by down-regulating components of the death-inducing signaling complex. Sci. Signal. 4, ra2. (2011).

【Term of Project】 FY2014-2018

【Budget Allocation】 150,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.lif.kyoto-u.ac.jp/labs/signal/