【Grant-in-Aid for Transformative Research Areas（B）】

Section III

Title of Project： Parametric biology based on translation rate regulatory mechanism

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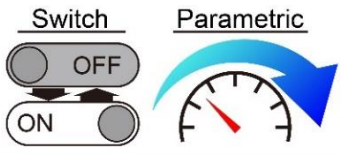
【Purpose of the Research Project】

Living organisms have "parametric" molecular mechanisms that allow them to respond flexibly to gradual changes. This is not a 0 or 1 on/off control, but a delicate control by "velocity change" of continuous response, that is often overlooked. In this study, we will focus on the concept of "variable translational speed", which is the core of parametric biology, a new field of life science. Four different research groups, possessing a hierarchical diversity from physical chemistry to physiology, will develop novel technologies to quantify and visualize the translation rate and utilize them mutually to clarify the still mysterious molecular mechanisms that regulate the translation rate from multiple perspectives. Our goal is to elucidate the role of parametric translation in the flexible control of life.

【Content of the Research Project】

Although molecular biology has identified the building blocks of life, and omics have described their quantitative nature, the mystery of the parametric control of biological functions, which lies behind the principle of flexibility of life, has been a major challenge in biological science.

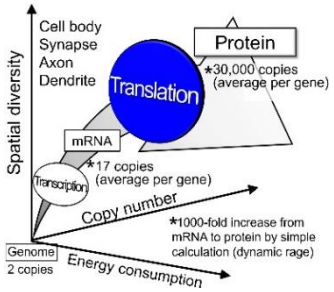
Changes in natural environment are usually continuous and gentle unless otherwise disaster. Similarly, organisms adapt to these alterations through the continuous conversion of the rate of reactions. Irrespective of this fact, the rapid "reset" response of the cellular state has been the major focus of previous research. It is therefore equally important to understand the parametric gradual regulation for the comprehension of the flexibility of life.



The concept of parametric rate regulation was proposed by Pittendrigh and Aschoff (1975), the founders of the circadian biology. It is a basic concept that can be extended to other biological mechanisms, though the molecular principles behind it remain unclear.

In this study, we will focus on "translation" to nail down the molecular mechanisms underlying the parametric control of numerous biological functions.

Since the dawn of molecular biology, it has been long assumed that translation is conducted through a static manufacturing machine, like a conveyor belt, without any dynamics. However, such a stereotype is now challenged. Recent innovations of next-generation sequencing uncovered the fact that translation has a huge dynamic range, changing its speed according to the conditions inside and outside of the cell. Particularly, the advent of Ribo-Seq, which counts the numbers of ribosomes along mRNAs, a technology to identify chemical modifications on RNA, the concept of subcellular translational regulation, and liquid-liquid phase separation by RNA-protein assembly are now challenging the traditional "copy number control"-nature of translation, rather raising an idea of parametric regulation of protein synthesis.



In this new framework, our team will conduct the following 4 projects: 1) Parametric control of sleep, metabolism, and circadian clock through the control of translation rate (Doi, Kyoto U), 2) Novel Disome-Seq: Comprehensive survey of parametric ribosomal stalling (Iwasaki, RIKEN), 3) Elucidation of the physicochemical regulation mechanism of subcellular parametric translation (Harada, Osaka U; Okabe, U Tokyo), and 4) Elucidation of parametric translation behind the flexible nature of nervous system (Ikeuchi, U Tokyo). In addition, we jointly develop new technologies to enable quantification and visualization of translation speed. Based on this foundation, we build a tight and collaborative team to drive the achievement of our common goals.

【Expected Research Achievements and Scientific Significance】

We expect our research will elucidate part of fundamental parametric regulation of life by reveling the intracellular mechanisms that underpin the flexible translation control. Since translation is an evolutionarily conserved and highly organized system, the knowledge and materials/methods obtained in this study will probably apply to widespread species and cellular contexts, including plants, fungi, and bacteria; cancer, brain, immunology, tissue regeneration, aging, metabolism, and so on.

【Key Words】

Parametric: speed control of biological functions

【Term of Project】

FY2020-2022

【Budget Allocation】

122,000 Thousand Yen

【Homepage Address and Other Contact Information】

http://parametric-translation.pharm.kyoto-u.ac.jp/
https://www.youtube.com/channel/UCL7n9ND9qnpxLCgVHGDpCyQ
doimasao@pharm.kyoto-u.ac.jp