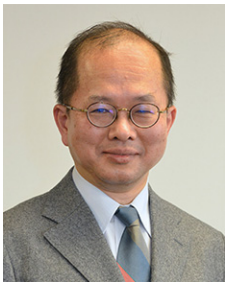
【Grant-in-Aid for Specially Promoted Research】

Biological Sciences



Title of Project：Physiological significance of ultradian oscillatory gene expression

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Research Project Number : 21H04976 Researcher Number : 80224369
Term of Project : FY2021-2025 Budget Allocation : 458,600 Thousand Yen
Keyword : ultradian oscillation, oscillator gene, neural stem cell, neural development, biological clock

【Purpose and Background of the Research】

Many forms of biological activity exhibit oscillatory gene expression with a few-hour periodicity, but the physiological significance of such oscillatory expression remains to be analyzed. During neural development, the transcriptional repressor Hes1 autonomously starts oscillatory expression by negative feedback in neural stem cells (NSCs), and Hes1 oscillations periodically repress other cell fate determination factors, thereby driving their oscillatory expression (Fig. 1). Cell fate determination factors induce cell differentiation when their expression is sustained but activate proliferation of NSCs when their expression oscillates. However, in addition to the importance of phase relationship between different oscillators and between neighboring cells, the detailed mechanisms of how oscillatory and sustained expression dynamics differentially control downstream events and how such different types of expression are controlled are unknown.

In this project, by using live-imaging and optogenetic gene control systems, we aim to answer these questions and will elucidate the physiological significance of ultradian oscillatory gene expression in biological events.

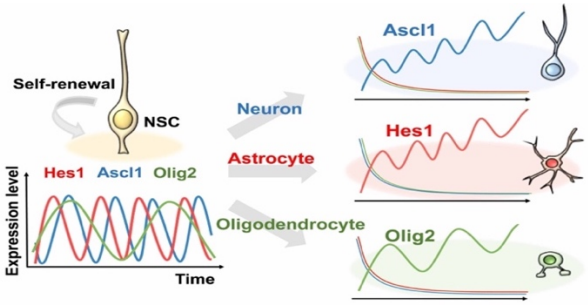

Fig. 1: Oscillatory gene expression in neural stem cells.

【Research Methods】

We plan to conduct the following projects.

(1) Oscillatory expression and cell cycle progression: NSCs proliferate more slowly when Hes1 expression is absent or sustained, and we plan to examine the relationship between Hes1 oscillation phase and cell cycle phase. We will also analyze the cell cycle genes that are controlled by Hes1 to elucidate the role of Hes1 oscillations in cell cycle progression.

(2) Oscillatory expression and a developmental clock: NSCs change their competency during neural development under the control of developmental clock genes, Hes1 and Hes5, but how their oscillations control the timing of switching NSC competency is unknown. We will analyze the relationship between Hes1 oscillation phase and the timing of switching NSC competency.

(3) The significance of out-of-phase oscillations between neighboring NSCs: To elucidate the significance of out-of-phase oscillations, using mouse ES cells carrying the Hes1 light-inducible system (Fig. 2), we will generate brain organoid under pulsatile blue light illumination to induce in-phase Hes1 oscillations. We will examine whether this treatment affects the diversity of neurons.

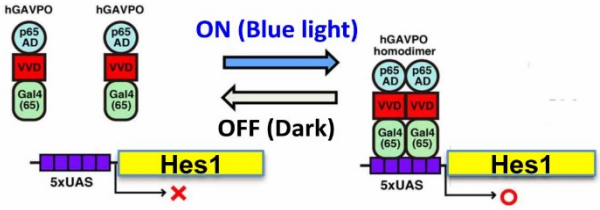

Fig. 2: Optogenetic Hes1-inducible system.

(4) Regulation of oscillatory versus sustained expression: By overexpressing embryonic-high genes and knocking down adult-high genes, we will identify a minimum gene set that can activate oscillations and elucidate the regulatory mechanism of oscillatory versus sustained gene expression.

【Expected Research Achievements and Scientific Significance】

Some genes exhibit different activity when their expression is oscillatory or sustained, and we will elucidate the mechanism of how such different expression dynamics differentially control downstream events. Our project will draw attention to the significance of ultradian oscillations of gene expression and bring great impact not only to the fields of stem cell research but also to more general fields of Biology.

【Publications Relevant to the Project】

- Yoshioka-Kobayashi, K., Matsumiya, M., Niino, Y., Isomura, A., Kori, H., Miyawaki, A., and Kageyama, R. (2020) Coupling delay controls synchronized oscillation in the segmentation clock. **Nature** 580, 119-123.
- Imayoshi, I., Isomura, A., Harima, Y., Kawaguchi, K., Kori, H., Miyachi, H., Fujiwara, T.K., Ishidate, F., and Kageyama, R. (2013) Oscillatory control of factors determining multipotency and fate in mouse neural progenitors. **Science** 342, 1203-1208.

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