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

Title of Project: **Dissection of Mammalian Biological Clock System at a Molecular Level**

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Research Area : Basic Biology
Keyword : Biological clock, circadian rhythm, signal transduction, neuroscience, photobiology

【Purpose and Background of the Research】

Most living organisms show a variety of rhythms by virtue of having an intrinsic time-measuring system, called circadian clock, which can be entrained to daily variation of the environmental conditions such as light-dark cycle. In mammals, the central clock system resides in the hypothalamic suprachismatic nucleus, and dysfunction of the central clock leads to mental diseases such as bipolar disorder and to instability of memory and emotion, suggesting that output signals from the central clock play unraveled roles in maintenance of brain functions. On the other hand, the light input pathway to the central clock plays a major role for its entrainment. The mammalian clock system employs intrinsically photosensitive retinal ganglion cells, together with rod and cone visual cells, as the photoreceptors. The molecular mechanism of how the light signals captured in those cells are converted to phase shifting signals remains to be elucidated. Lastly, the core oscillating machinery in the circadian clock involves a number of clock genes and their encoded proteins, which generate a molecular oscillation with a transcription/translation-based feedback regulation. A key question is the mechanism of how these clock genes and proteins generate the very slow and stable molecular oscillation with a period of approx. 24 hours. The goal of this study is to understand the molecular and neuronal mechanisms that underlie the circadian clock function with its input and output regulation.

【Research Methods】

To understand the mechanism of circadian clock in terms of both behavioral rhythms and molecular oscillation, we will focus on the following three projects on the clock components. [1] Input pathway: The circadian clock generates "robust" 24-hour rhythms, while its phase can be "flexibly" controlled by environmental factors. To understand the mechanism underlying the robustness and flexibility, we will dissect molecular basis of clock phase regulation by the input pathways. [2] Output pathway: Higher-ordered functions in the brain are likely to be controlled by output signals of the circadian clock system. We will explore physiological roles of the clock output signals that are essential for brain functions. [3] Molecular Oscillator: Most of the clock proteins essential for circadian oscillation are regulated by post-translational modifications. We will investigate the roles of the modifications in spatiotemporal regulation of the clock proteins in order to understand how the slow and stable molecular oscillation is achieved.

【Expected Research Achievements and Scientific Significance】

In humans, nocturnal activities and midnight meals are known to disturb biological clock system, leading to obesity and other metabolic disorders. Shift works often elicit mood disorder. These facts suggest an intimate interaction between the circadian clock and normal physiological functions. However, their molecular links are largely elusive. The researches in this project will provide clues to understanding the chronobiological basis of human health and diseases.

【Publications Relevant to the Project】

Kon, N. *et al.* (2008) Activation of TGF-ß/activin signalling resets the circadian clock through rapid induction of *Dec1* transcripts. *Nature Cell Biol. 10*, 1463-9.

Hatori, M. *et al.* (2011) Light-dependent and circadian clock-regulated activation of sterol regulatory element-binding protein, X-box-binding protein 1 and heat shock factor pathways. *Proc. Natl. Acad. Sci. USA. 108*, 4864-9.

Yoshitane, H. *et al.* (2012) JNK regulates the photic response of the mammalian circadian clock. *EMBO Rep. 13*, 455-61.

【Term of Project】 FY2012-2016

【Budget Allocation】 167,200 Thousand Yen

【Homepage Address and Other Contact Information】

http://www.biochem.s.u-tokyo.ac.jp/fukada-lab/index-j.html
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