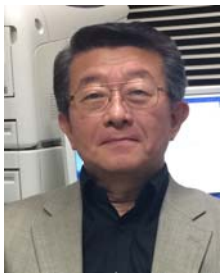
【Grant-in-Aid for Specially Promoted Research】

Biological Sciences



Title of Project : Molecular dissection of robust and flexible circadian clock and its control of animal physiology

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Research Project Number : 17H06096 Researcher Number : 80165258
Research Area : Biology: Basic biology, Biological science
Keyword : Animal physiology and biochemistry, Transcriptional regulation, Post-translational modification, Circadian rhythm, Circadian oscillation mechanism

【Purpose and Background of the Research】

The circadian clock that governs daily rhythms in behaviors and physiology is characterized by its robustness of regulating stable daily rhythms. On the other hand, the circadian clock flexibly responds to a variety of external and internal signals in order to adjust its phase appropriately. In this project, we would explore a new mechanism that enables the stable oscillation of the molecular clock. We would also pursue a molecular mechanism that supports the flexibility of the entrainment.

In the later phase of this 5-years project, we would pay our attention toward interaction between the circadian clock and senescence. In addition to the well-recognized notion that the circadian clock is weakened during aging, a new idea will be examined whether aging could be one of the output of the circadian clock deformation. We would investigate bi-directional interaction between the circadian clock oscillation and aging.

【Research Methods】

In this project, we would perform extensive researches at molecular and cellular levels, and the outcomes will be fed back into behavioral analyses of mice that are genetically engineered or subjected to surgical or pharmacological manipulations. Based on the results obtained in the earlier phase of this project, we would make efforts to develop our research to the understanding of relationship of senescence and change in circadian clockwork during aging. Particularly we will explore molecular mechanism underlying bi-directional control between aging and circadian clock.

【Expected Research Achievements and Scientific Significance】

In individual cells, the clock genes and their encoding clock proteins form transcriptional and translational feedback loops, which generate a wide variety of oscillating transcripts. However, only a part of these oscillating transcripts has been recently shown to oscillate at the transcription level, while many other transcripts were constant at the de novo transcription (Koike *et al.,* 2012; Menet *et al.,* 2012). These observations strongly suggested important roles of post-transcriptional regulation in generating rhythmic transcripts, and indeed we have found an important role of A-to-I RNA editing rhythm (Terajima *et al.*, 2017). Furthermore, a number of studies such as Hirano *et al.* (2013) demonstrated that the robust and stable oscillation of the circadian clock requires post-translational modifications of the clock proteins, such as phosphorylation and ubiquitination. The protein modifications regulate the clock proteins in various aspects, such as their stabilities, cellular localization profiles, transcriptional activities, and protein-protein interactions. In this project, we would investigate potential roles of these unexplored steps of clock regulation toward understanding of the stable and flexible properties of the circadian clock at the molecular and cellular levels.

【Publications Relevant to the Project】

・Hirano *et al.* (2013) FBXL21 regulates oscillation of the circadian clock through ubiquitination and stabilization of cryptochromes. ***Cell***, *152,* 1106-1118
・Terajima, Yoshitane *et al.* (2017) ADARB1 catalyzes circadian A-to-I editing and regulates RNA rhythm. ***Nature Genet.*** *49,* 146-151

【Term of Project】

FY2017-2021

【Budget Allocation】

435,800 Thousand Yen

【Homepage Address and Other Contact Information】

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