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

Section III

Title of Project： Chrono-proteinology: principle and design for protein timers

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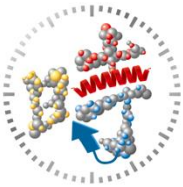
Number of Research Area：21B303 Researcher Number：70569920

【Purpose of the Research Project】

There are various time scales in biology such as longevity, seasonal responses, circadian rhythmicity, developmental processes, cell division cycles, and heartbeats. In other words, living organisms consists of different time scales. What are the mechanisms for measuring “time” that correspond to each event at different time scale?

To tackle this question, we will focus on proteins responsible for molecular mechanisms that directly regulate time information. We have named this research area as "Chrono-proteinology". We believe that the physical properties and dynamics of proteins generate “time” on various time scales as autonomous protein oscillators. The dynamics includes protein-protein interactions, post-translational modifications, enzymatic activities, and conformational changes.



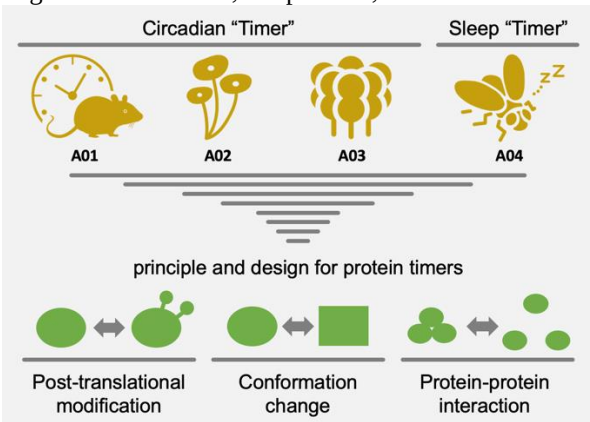
The left logo represents the Chinese/Japanese character "Kanzi" for the word "Time" (時). Each part of the Kanzi is composed of protein structures such as alpha-helix and beta-sheet. You can also see "day (日)" in yellow, "earth (土)" in red, and "sun, a traditional Japanese unit for length (寸)" in blue, which look like a protein trimer.

【Content of the Research Project】

Nobel Prize in Physiology or Medicine in 2017 was awarded to three researchers, who discovered the molecular mechanism of circadian clock system in fruit fly. They proposed that the expression of clock genes including *period* and *timeless* are controlled by negative feedback loop via transcription and translation of themselves. However, the negative feedback loop dogma is not applicable to all circadian systems across phyla: for example, enucleated *Acetabularia* which should not have the transcriptional rhythms maintains circadian rhythmicity. Furthermore, in prokaryotic cyanobacteria, autonomous protein-phosphorylation rhythmicity is observed when KaiC protein is incubated with KaiA, KaiB, and ATP *in vitro*. Although KaiC is not conserved in eukaryotes, we will pursue the possibility that proteins, of which function is analogous to KaiC define the time scale also in eukaryotes, while transcriptional feedback plays the role to generate outputs of the clock function. In other words, when the transcriptional feedback is removed, the clock appears to stop at a glance (because of the lack of hands of the clock), but clock oscillators (quartz of the clock) may continue to measure the time through protein-protein interactions, post-translational modifications, enzymatic activities, and conformational changes. When we think of protein dynamics generating the time information in this way, similar mechanisms might also lie in biological phenomena other than circadian rhythms. Group A01 will analyze the protein rhythms of the circadian clock. Group A02 will understand the mechanism of circadian rhythms in the enucleated *Acetabularia*. Group A03 will search for KaiC homologs in eukaryotes. Group A04 will approach the time of sleep through understanding the protein properties of “Nemuri”.

【Expected Research Achievements and Scientific Significance】

If the cellular timer for the circadian rhythms is identified and extracted at the protein level, this research field will lead emerging field of biochemistry and biophysics that also have cellular time information. Furthermore, the vision provided by this Chrono-proteinology may be the antithesis of the concept originated from the central dogma that it is DNA, not proteins, that determines traits.



【Key Words】

Chronoproteinology: The concept that protein dynamics, such as protein-protein interactions, post-translational modifications, enzymatic activities, and conformational changes, generate "time" on various time scales.

【Term of Project】 FY2021-2023

【Budget Allocation】 104,700 Thousand Yen

【Homepage Address and Other Contact Information】

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