A New Epoch in Circadian Rhythm Research

Discovery of a Novel Gene of Circadian Rhythm and Investigating Its Mechanism

Professor Joonho Choe (Department of Biological Sciences)

Professor Choe's research team has discovered a circadian rhythm gene, twenty-four (tyf), in *Drosophila* and has revealed that regulation of the translational phase of protein synthesis is paramount in the mechanism leading to the function of the biological clock. The findings of his research were published in Nature.

On Earth, we experience night and day as a result of the Earth rotating on its axis, which also brings about changes in light intensity, temperature, and so on. In order to adjust to such changes, humans, fruit flies, mice, and many more living organisms are 'equipped' with biological clocks that function on a circadian rhythm. A circadian biological clock enables and regulates various biological processes taking place in the body on a 24-hour cycle, even in the absence of external cues such as heat and light. However, once information on actual time is provided through such external cues, the biological clock resets itself to synchronize to the cycle in which the environment changes.

When we travel abroad, we often experience jet lag, which subsides after a few days. This is part of the process where our internal biological clock synchronizes itself to the new time zone. The circadian rhythm is known to be an important factor in controlling sleep in organisms. For example, the advanced sleep phase syndrome is a sleep disorder related to the biological clock, which causes the patient to go to sleep and wake up very early.

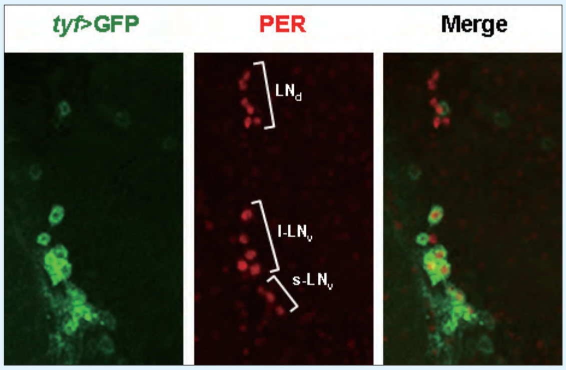
Professor Choe's research team carried out experiments on *Drosophila*. Fruit flies are widely used in biological rhythm research due to the ease in multiplying them. It is also relatively simple to carry out genetic experiments on them and, above all, their biological clock system is very similar to that of humans and mice. The *Drosophila*'s brain contains neurons that control the biological rhythm, and each of the neurons has its own 'molecular clock' and is thus able to create a circadian rhythm. Six genes play a major role in this 'clockwork', whereby they function in relation to each other as different components of a common clock in order to maintain a biological clock system that can function even in the absence of external cues. These genes are regulated over several stages: assembly of transcriptional elements, posttranslational regulation such as phosphorylation, and protein disassembly. Adult fruit flies usually emerge from pupae in the early morning, and are able to estimate the change in light intensity in advance and show high activity before dawn and dusk. They also exhibit 24-hour circadian behavior in constant absence of light.

Discovering the Link between *Drosophila* Biological Rhythms and Protein Translation

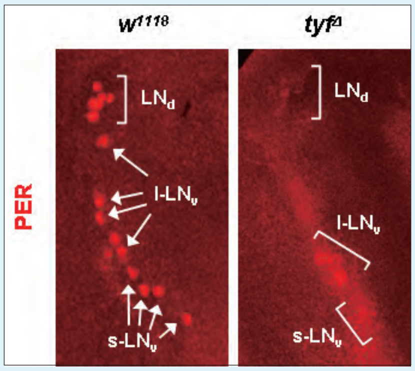
Professor Choe's research team set out to search for the genes responsible for biological rhythm, and observed the routine daily behaviors of flies using a transgenic *Drosophila* mutant library. The team carried out an experiment in which a group of flies were first exposed to an environment that alternated between bright and dark every 12 hours, and were then kept in a completely dark environment for seven days. The flies were observed using a *Drosophila* activity monitor. An analysis of their movements and behaviors showed that some of the flies had become less periodical compared to naturally-found flies, and that their rhythm had lengthened compared to the 24-hour circadian rhythm. Professor Choe argued that such changes in behavior were due to a gene he and his team discovered, which they named 'twenty-four'. Through genetic testing and behavior analyses, the team proved that proper expression of twenty-four in the clock cells of the fly's brain plays a significant role in maintaining the circadian rhythm. In addition, by investigating the interaction between the different genes that are required for rhythm regulation, the team proved that translation of period by twenty-four (the stage at which proteins are produced using the information in genes) is part of the *Drosophila* biological clock regulation mechanism. Research on *Drosophila* biological rhythm has mostly focused on transcriptional and posttranslational regulation, the latter of which has received even less attention. However, this study has exhibited the importance of the twenty-four gene and its interactions with several proteins during its translation, hence providing a link between *Drosophila* biological rhythm and translation mechanisms.

◎ Implications and Future Prospects

Professor Choe has successfully demonstrated that regulation of translation is closely related to biological clock mechanisms. Due to high possibilities of extrapolating the research results onto mice, and further onto humans, this study will contribute greatly to research on the biological rhythms of higher organisms, as well as to finding solutions to sleeping disorders caused by impaired biological rhythms.



01



02

01 Twenty-four (tyf) and PERIOD (PER) expression within *Drosophila* brain.

02 Decreased expression of PERIOD in *Drosophila* with mutant twenty-four genes.

● **Research Funding** | Ministry of Education, Science and Technology, 21C Frontier R&D Program
● **Publication** | Lim, C., Lee, J., Choi, C., Kilman, V. L., Kim, J., Park, S. M., Jang, S. K., Allada, R., and Choe, J. "The Novel Gene Twenty-Four Defines a Critical Translational Step in the *Drosophila* Clock," *Nature* 470 (2011):399–403.