KYUSHU UNIVERSITY

Public Relations Initiative, Kyushu University
744 Motooka Nishi-ku Fukuoka, 819-0395
TEL: +81-92-802-2443 FAX: +81-92-802-2139
E-MAIL: sysintlkh@jimu.kyushu-u.ac.jp
URL: https://www.kyushu-u.ac.jp

PRESS RELEASE (2025/6/13)

Scientists discover the 'ticking' mechanism driving nature's simplest circadian clock

New research reveals that circadian clock protein KaiC regulates phosphorylation to keep time in cyanobacteria.

Aichi, Japan—Researchers from the Institute for Molecular Science (IMS)/SOKENDAI and Kyushu University have uncovered the molecular mechanism that drives the "ticking" of the circadian clock in cyanobacteria. Their study reveals how a clock protein called KaiC controls chemical reactions with remarkable precision, acting like the hand of a clock that waits, then moves at just the right moment. The findings were published in *PNAS Nexus* on April 28, 2025.

To adapt to Earth's daily rotation, most living organisms, from simple, single-celled bacteria to complex, multicellular mammals, have evolved internal timekeeping systems known as circadian clocks. Among all known species, only cyanobacteria possess a circadian clock system that scientists have been able to fully reproduce in a test tube. This system involves three proteins, KaiA, KaiB, and KaiC. When mixed in a test tube, KaiC undergoes a cycle of phosphorylation and dephosphorylation, a rhythmic attachment and detachment of phosphate groups that repeats every 24 hours, just like a clock (Figure 1A). Despite decades of study, a key mystery remained. How exactly does the phosphate attach to KaiC? In other words, what drives the motion of the clock's hand?

To answer this question, the research team, led by Assistant Professor Yoshihiko Furuike and Professor Shuji Akiyama from IMS/ SOKENDAI, and Associate Professor Toshifumi Mori from the Institute for Materials Chemistry and Engineering, Kyushu University, focused on KaiC in isolation, without KaiA and KaiB. This simplified system enabled direct observation of the phosphorylation process. Contrary to previous assumptions, they discovered that even alone, KaiC can slowly bind phosphate, indicating that the fundamental "ticking" of the clock resides within KaiC itself (Figure 1B).

Using the structural data of KaiC obtained at near-atomic resolution, the team simulated the chemical reaction of phosphorylation through molecular dynamics and quantum chemical simulations. This method allowed them to observe how a phosphate group gradually approaches and binds to KaiC (Figure 1C).

The team found that subtle shifts in the arrangement of certain amino acids, specifically glutamate and arginine residues, serve as molecular triggers. These residues effectively control whether the phosphate group can bind, thereby pausing or permitting the reaction like a timed gate. In other words, KaiC holds the clock hand steady until the precise moment it should tick.

The mechanism discovered in this study is not limited to cyanobacteria. Many organisms, including humans, rely on phosphorylation to regulate their internal clocks. This research thus provides fundamental insights into the universal logic of biological timekeeping.

Moreover, since phosphorylation is related to various diseases, understanding how proteins control the timing of chemical reactions may have far-reaching applications in biomedicine and drug design. While this study focused on the phosphorylation process, dephosphorylation remains less well understood and is a key topic for future investigation.

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The full release from Institute for Molecular Science (IMS) can be found here: https://www.ims.ac.jp/en/news/2025/06/0613.html

For more information about this research, see "The priming phosphorylation of KaiC is activated by the release of its autokinase autoinhibition" Yoshihiko Furuike, Yasuhiro Onoue, Shinji Saito, Toshifumi Mori, Shuji Akiyama, *PNAS Nexus*, https://doi.org/10.1093/pnasnexus/pgaf136

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutes of higher education, consistently ranking as one of the top ten Japanese universities in the Times Higher Education World University Rankings and the QS World Rankings. The university is one of the seven national universities in Japan, located in Fukuoka, on the island of Kyushu—the most southwestern of Japan's four main islands with a population and land size slightly larger than Belgium. Kyushu U's multiple campuses—home to around 19,000 students and 8000 faculty and staff—are located around Fukuoka City, a coastal metropolis that is frequently ranked among the world's most livable cities and historically known as Japan's gateway to Asia. Through its VISION 2030, Kyushu U will "drive social change with integrative knowledge." By fusing the spectrum of knowledge, from the humanities and arts to engineering and medical sciences, Kyushu U will strengthen its research in the key areas of decarbonization, medicine and health, and environment and food, to tackle society's most pressing issues.

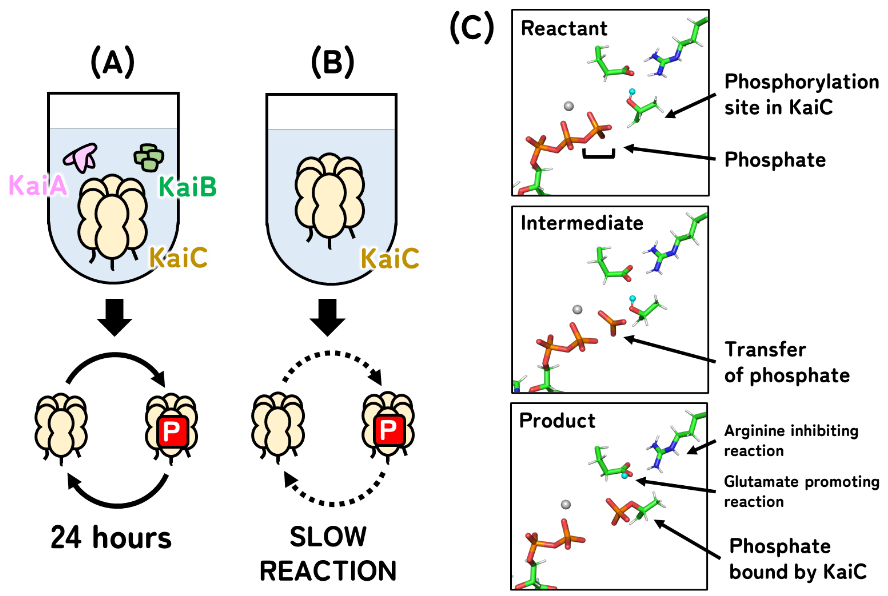

Fig. 1. Visualization of phosphorylation in KaiC. (Credit: Yoshihiko Furuike, Restriction: News organizations may use or redistribute this image, with proper attribution, as part of news coverage of this paper only.)

[Contact]
Toshifumi Mori, Associate Professor
Institute for Materials Chemistry and Engineering, Department of Applied Molecular Chemistry
Tel: +81-92-583-7800
E-mail: toshi_mori@cm.kyushu-u.ac.jp