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PRESS RELEASE (2026/06/11)

Body clock found to control inflammatory responses in macrophages

Body clock regulator BMAL1 transports a fatty acid-oxidation enzyme into the cell nucleus, triggering macrophage inflammation, opening possibilities for time-based therapies

Fukuoka, Japan—Daily life is shaped by the solar day, influencing when we wake up, eat, work, and sleep. Inside the body, a similar internal timing system—present in nearly every cell—known as the circadian clock, synchronizes many biological functions, such as sleep, metabolism, hormone release, and even the immune system's activity. Now, researchers from Kyushu University have uncovered a previously unknown mechanism by which the circadian clock protein called brain and muscle ARNT-like 1 (BMAL1) enhances inflammatory responses in immune cells. The findings offer new insights into how the body clock influences immune responses and may pave the way for new approaches to treating inflammatory diseases and cancer.

When our body encounters an injury or infection, the immune system sends out cells known as macrophages to initiate an inflammatory response that begins the healing process. These macrophages can exist in two different states: a pro-inflammatory (M1) state, which promotes inflammation, and an anti-inflammatory (M2) state, which helps resolve inflammation and repairs the tissue. The balance between these two states is important, as disruptions can lead to uncontrolled inflammation, which in turn can give rise to chronic inflammation-associated diseases, including cancer, liver disease, diabetes, and autoimmune disorders.

Previous studies have revealed that macrophage activity is closely linked to the circadian clock, with BMAL1 playing a central role in regulating this process. In a study published in the journal *Cell Reports* on June 9, 2026, a research team comprising Lecturer Akito Tsuruta, Professor Naoya Matsunaga, Professor Satoru Koyanagi, and Specially Appointed Professor Shigehiro Ohdo from Kyushu University's Faculty of Pharmaceutical Sciences has found that BMAL1 drives macrophages toward a pro-inflammatory M1 state by activating inflammatory signaling pathways in the cell nucleus.

"We discovered a fundamentally new concept that the circadian clock controls inflammation not only through direct transcriptional regulation but also through nuclear lipid metabolism. This concept links the body clock to intracellular metabolism and to immune function," says Tsuruta.

To investigate the role of BMAL1 in macrophage inflammation, the researchers generated macrophage-specific BMAL1-deficient mice and exposed them to the chemical carcinogen diethylnitrosamine, which induces liver inflammation and tumor formation.

The team observed that normal mice showed a marked increase in pro-inflammatory M1 macrophages along with elevated inflammatory signals after the exposure. In contrast, mice lacking BMAL1 in their macrophages showed significantly reduced inflammation and suppressed liver tumor development.

To understand the molecular basis of these effects, the team analyzed proteins that interact with BMAL1 in the nucleus using mass spectrometry. Their experiments revealed that BMAL1 binds to multi-functional protein 2 (MFP2), a fatty acid-oxidation enzyme normally found in cellular compartments called peroxisomes, and transports it into the cell nucleus. Once inside the nucleus, MFP2 increases acetyl-CoA levels, which drives acetylation of key proteins, including p65, a component of the transcription factor NF-κB, a key regulator of inflammatory genes. This activates NF-κB, which functions as a switch for inflammatory genes, thereby driving macrophages into the pro-inflammatory M1 state.

Notably, nuclear MFP2 levels fluctuate according to the time of day in a BMAL1-dependent manner. In the livers of the control mice, nuclear MFP2 increased during periods when BMAL1 levels were the highest, while this rhythmicity disappeared in BMAL1-deficient mice.

These findings suggest that targeting or blocking nuclear MFP2 and administering drugs at an optimal time of the day could become a new therapeutic strategy for chronic inflammatory diseases and enhance treatment efficacy while minimizing side effects.

“In the future, we aim to validate this mechanism in human cells and tissue samples. In addition, we aim to explore whether drug administration at the time when nuclear MFP2 levels peak can help improve outcomes in models of inflammatory disease and cancer,” concludes Tsuruta.

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For more information about this research, see "The circadian clock component BMAL1 enhances inflammatory response of macrophages by nuclear transport of peroxisomal β-oxidation enzyme MFP2,” Akito Tsuruta, Nodoka Hirao, Megumi Shibata, Yuya Yoshida, Yoshihiro Izumi, Naoya Shindo, Yuki Shiiba, Kazuhiro Higashi, Takuto Inoki, Yuichiro Kai, Yasuha Hiraoka, Tomoaki Yamauchi, Akio Ojida, Takeshi Bamba, Naoya Matsunaga, Satoru Koyanagi, and Shigehiro Ohdo, *Cell Reports*, https://doi.org/10.1016/j.celrep.2026.117480

About Kyushu University

Founded in 1911, Kyushu University is one of Japan's leading research-oriented institutions 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. Located in Fukuoka, on the island of Kyushu—the most southwestern of Japan’s four main islands—Kyushu U sits in a coastal metropolis frequently ranked among the world’s most livable cities and historically known as Japan’s gateway to Asia. Its multiple campuses are home to around 19,000 students and 8,000 faculty and staff. 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.

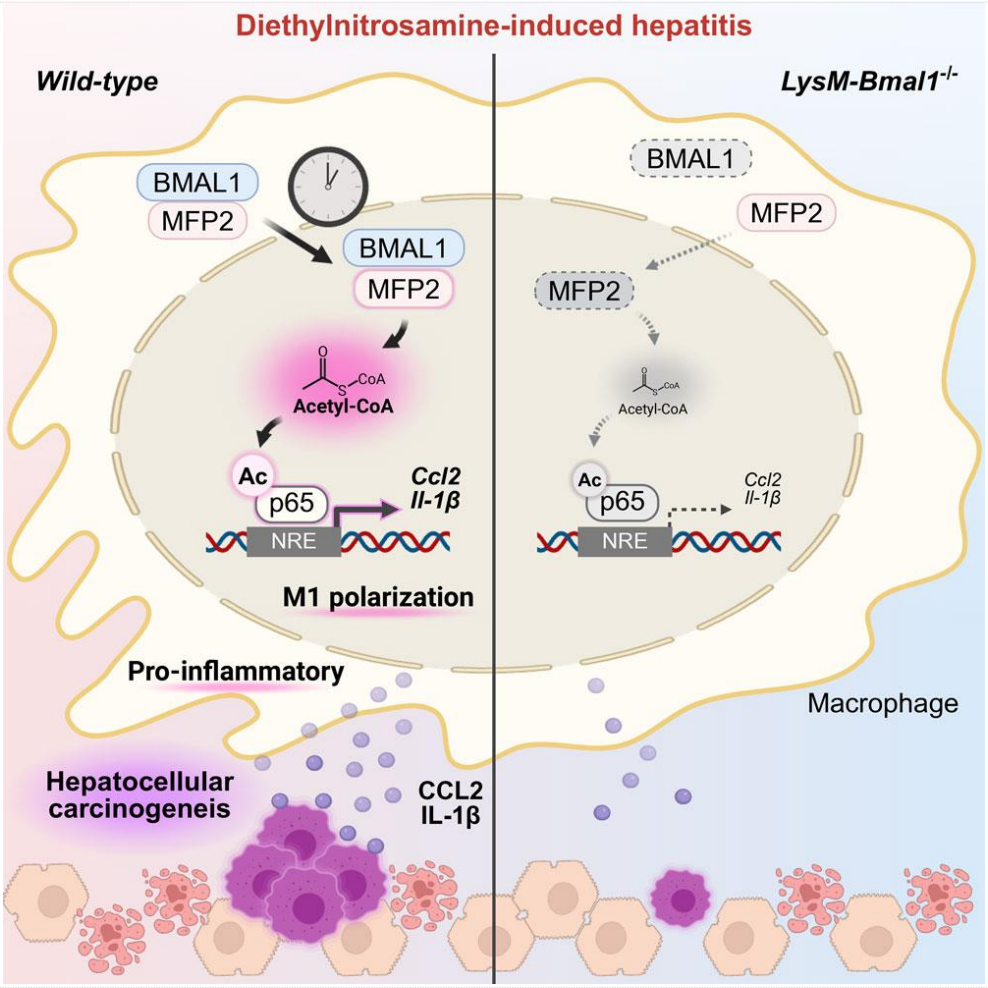

Fig. 1. Mechanism of brain and muscle ARNT-like 1 (BMAL1)-dependent inflammatory responses in macrophages
Using mouse models, researchers from Kyushu University found that BMAL1 transports the fatty acid-processing enzyme multi-functional protein 2 into the nucleus, where it enhances inflammatory gene activity through nuclear factor-kappa B signaling.

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