Researchers identify how body clock affects inflammation

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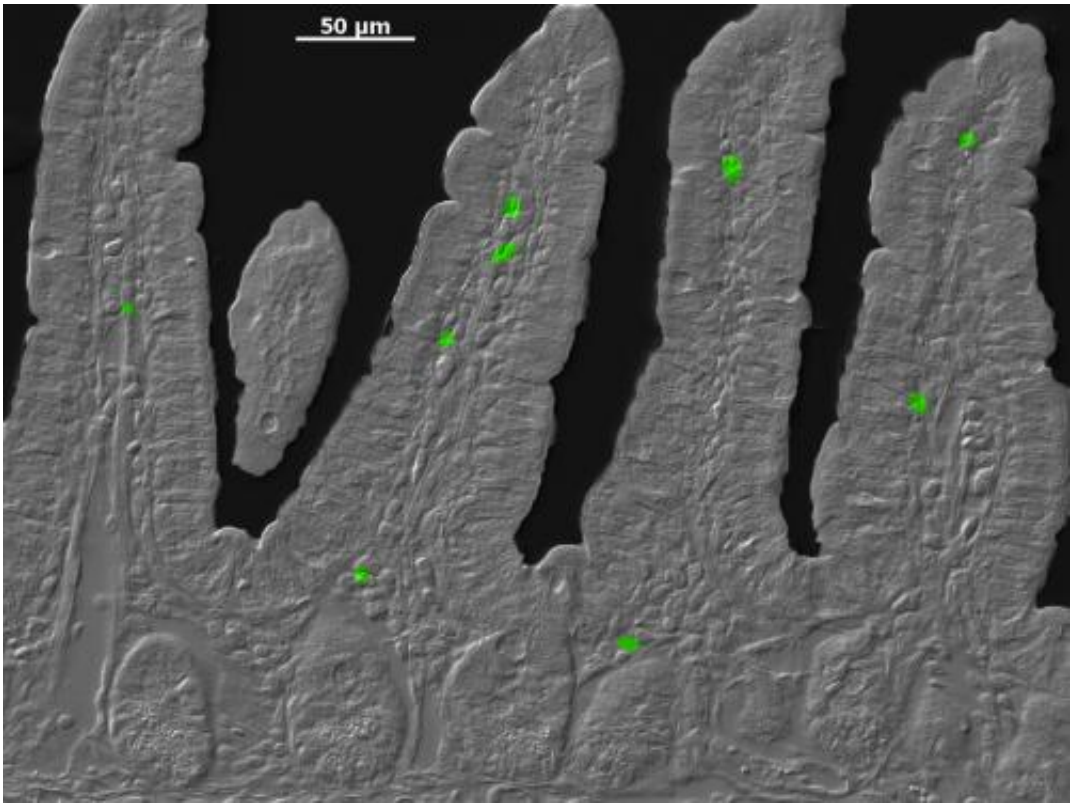


Th17 cells in the intestine. This paper shows that the development of these cells is regulated by the circadian clock. Frozen intestinal sections were stained with anti-CD4-fluorescein isothiocyanate (FITC) and anti-RORγt-phycoerythrin (PE) to identify Th17 cells. A differential interference contrast image of the same field was overlaid with the fluorescence image to locate Th17 cells, which were then highlighted by pseudocoloring in Photoshop. Credit: Xiaofei Yu, Shipra Vaishnava and Yuhao Wang

UT Southwestern Medical Center researchers report that disrupting the light-dark cycle of mice increased their susceptibility to inflammatory disease, indicating that the production of a key immune cell is controlled by the body's circadian clock.

The study published in the Nov. 8 edition of *Science* identifies a previously hidden pathway by which the body's circadian clock controls the numbers of key inflammatory cells called interleukin-17-producing CD4+ T helper cells (T_H17). The work could lead to new ways to rev up the body's immune response to infection or dampen that response in the case of autoimmune diseases in which the body attacks its own tissues, said senior author Dr. Lora Hooper, Professor of Immunology and Microbiology and a Howard Hughes Medical Institute (HHMI) Investigator.

Co-authors include Neuroscience Chair and HHMI Investigator Dr. Joseph Takahashi, whose discovery of the mouse and human clock genes led to a description of a conserved circadian clock mechanism in animals. The lead author is Xiaofei Yu, an Immunology student in the UT Southwestern Graduate School of Biomedical Sciences.

"Virtually all life forms on Earth undergo physiological and behavioral changes on a 24-hour daily, or circadian, cycle in accordance with the changes in natural light. Human beings are no exception. Many of our physiological processes, such as eating and sleeping, vary dramatically between day and night. Such processes are controlled by a group of proteins, collectively termed the 'circadian clock,' which function together in individual cells, capturing light cues from the visual and nervous systems and using these cues to regulate gene expression," explained Dr. Hooper, who holds appointments in the Center for the Genetics of Host Defense and the Cancer Immunobiology Center.

Although the circadian clock is known to regulate metabolism and sleep-

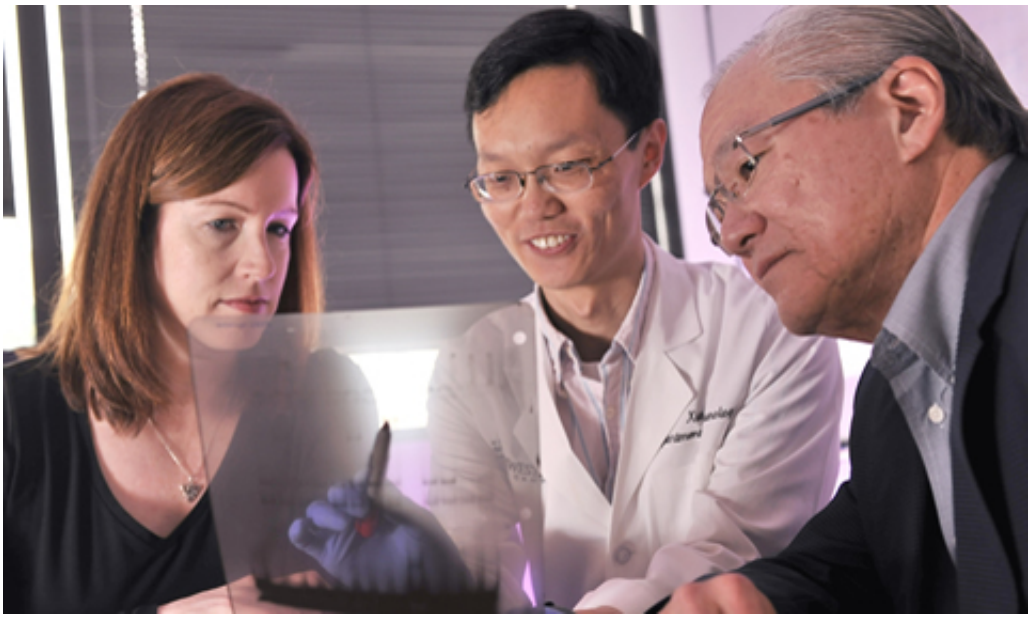
wake cycles, little was known about whether the circadian clock also regulates the immune system, the body's defense against infectious viruses and bacteria, she said.

Using a mouse model, the researchers identified a gene called *Nfil3*, which guides the development of the T_H17 cells that patrol mucosal surfaces like the intestinal lining and protect against bacterial and fungal infections.

"However, if their numbers are not controlled properly, T_H17 cells can produce too much friendly fire and lead to inflammatory diseases such as inflammatory bowel disease (IBD), which afflicts about 600,000 Americans each year," Dr. Hooper said.

"We found that *Nfil3* regulates T_H17 development by controlling the cellular supply of a protein in T cells called Rorγt that directs the cells to develop into T_H17 cells. In mice, the amount of Rorγt in T cells changes during the day-night cycle and is higher at noon than at midnight. This fluctuation causes more T_H17 cells to develop at noon when the mice are sleeping," she said.

Mice are nocturnal, meaning their sleep-wake times are the opposite of those in humans.



From left: Dr. Lora Hooper, Xiaofei Yu, and Neuroscience Chair Dr. Joseph Takahashi are studying how the body clock affects inflammation. Credit: UT Southwestern Medical Center

"When we disrupted the normal day-night light cycles of mice, essentially giving them jet lag, we found that too many T_H17 cells developed and accumulated in the intestines. As a result, these mice were more prone to develop an IBD-like disease, due to friendly fire from the overabundance of those inflammatory T_H17 cells," she said, adding that it took more than a single day's disruption to change the T_H17 concentrations.

Dr. Hooper stressed that it is too soon to tell if the same thing is happening in people, but the possibility is worth studying.

The researchers point out that modern life often involves chronic circadian disruptions, such as night-shift work or jet lag, that other research studies have linked to human inflammatory disease.

"Our findings suggest that the pathologic consequences of circadian disruption may be due in part to direct interactions between the circadian clock and the pathways that regulate proinflammatory immune cell development," the researchers conclude.

More information: "TH17 Cell Differentiation Is Regulated by the Circadian Clock," by X. Yu et al. *Science*, 2013.

Provided by UT Southwestern Medical Center