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Being sick in the morning can be different from being sick at night

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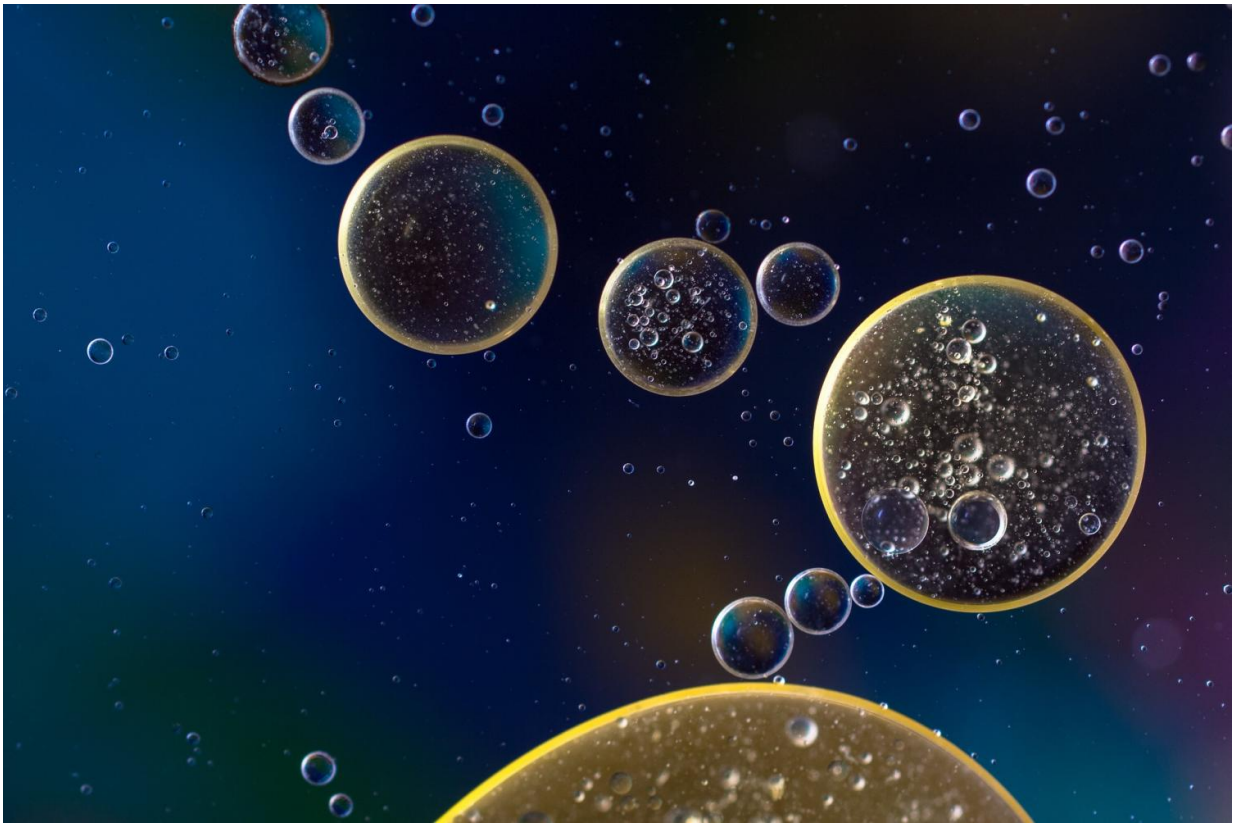

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In a review published May 17 in the journal *Trends in Immunology*, researchers discuss how time of day affects the severity of afflictions ranging from allergies to heart attacks.

Researchers in Switzerland compiled studies, predominantly in mice, that looked at the connection between circadian rhythms and immune responses. For example, studies showed that adaptive immune responses—in which highly specialized, pathogen-fighting cells develop over weeks—are under circadian control. This is "striking," says senior author Christoph Scheiermann, an immunologist at the University of Geneva, "and should have relevance for clinical applications, from transplants to vaccinations."

The body reacts to cues such as light and hormones to anticipate recurring rhythms of sleep, metabolism, and other physiological processes. In both humans and mice, the numbers of white blood cells also oscillate in a circadian manner, raising the question of whether it might be possible one day to optimize immune response through awareness and utilization of the circadian clock.

In separate studies that compared immune cell time-of-day rhythms under normal conditions, inflammation, and disease, researchers found that:

- Heart attacks in humans are known to strike most commonly in the morning, and research suggests that morning heart attacks tend to be more severe than at night. In mice, the numbers of monocytes—a type of white blood cell that fights off bacteria, viruses, and fungi—are elevated in the blood during the day. At night, monocytes are elevated in infarcted heart tissue, resulting in decreased cardiac protection at that time of day relative to morning.
- The ability of immune cells to fight atherosclerotic plaques can depend on CCR2—a chemokine protein linked to immune function and inflammation. CCR2 exhibits a daily rhythm in mice, peaking in the morning, and based on its influence on immune cells, can be followed to understand white blood cell

behaviors in mouse models of atherosclerosis.

- Parasite infections are time-of-day dependent. Mice infected with the gastrointestinal parasite Trichuris muris in the morning have been able to kill worms significantly faster than mice infected in the evening.
- A bacterial toxin tied to pneumonia initiates an inflammatory response in the lungs of mice. Recruitment of immune cells during lung inflammation displays a circadian oscillation pattern. Separately, more monocytes can be recruited into the peritoneal cavity, spleen, and liver in the afternoon, thus resulting in enhanced bacterial clearance at that time.
- Allergic symptoms follow a time-of-day dependent rhythmicity, generally worse between midnight and early morning. Hence, the molecular clock can physiologically drive innate immune cell recruitment and the outcomes of asthma in humans, or airway inflammation in mice—the review notes.

"Investigating circadian rhythms in innate and adaptive immunity is a great tool to generally understand the physiological interplay and time-dependent succession of events in generating immune responses," Scheiermann says. "The challenge lies in how to channel our growing mechanistic understanding of circadian immunology into time-tailored therapies for human patients."

More information: Robert Pick et al, Time-of-Day-Dependent Trafficking and Function of Leukocyte Subsets, *Trends in Immunology* (2019). DOI: 10.1016/j.it.2019.03.010

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