Researchers determine key element in circadian clock speed

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Credit: Vera Kratochvil/public domain

In a discovery that may lead to new treatments for sleep disorders, jet lag and other health problems tied to circadian rhythms, researchers at Dartmouth's Geisel School of Medicine have identified a determinant of the circadian clock's period. Their findings appear in the January 29th issue of *Science*.

Whether in fungi or human beings, circadian clocks influence nearly all aspects of an organism's life. On a molecular level at the core of these circadian rhythms, biological oscillators are present and key proteins comprising these cycles have a lifetime of approximately 24 hours. Because the period of the clock matched the lifetime of the proteins it was assumed for many years that the stability of the protein determined the period length of these biological clocks. But it's not that simple.

Why this turnover occurs within 24 hours has long been attributed to the clock proteins themselves, which undergo coordinated and progressive modification—actually phosphorylation, which modifies protein structure and activity—leading to degradation and turnover. Essentially, clock proteins are slowly phosphorylated until they become unstable and disappear allowing the cycle of synthesis and destruction to start again.

By examining in a well known model organism the factors leading to period determination—and the longstanding causal loop uniting clock protein phosphorylation with stability—Dartmouth researchers have pinned down the determinant of the clock's period.

"We all used to think the circadian cycle ended when the important clock protein was degraded," says Principal Investigator Jay Dunlap, PhD, professor of genetics and biochemistry and chair of the Department of Genetics, "and that period length was determined in large part by how stable those proteins were."

But Dunlap's team, in work supported by the U.S. National Institute of General Medical Sciences and done in collaboration with the lab of Luis Larrondo from the Pontificia Universidad Católica de Chile, found that phosphorylation itself was sufficient to change the effectiveness of the protein in the negative feedback of the oscillator so that the clock protein was no longer effective in feedback. Although protein degradation is the final outcome, protein structure, not changes in stability, may actually be the key element determining clock speed.

"Surprisingly, we found that stability is not the key factor in period determination," Dunlap says. "Once phosphorylation has passed a certain point it doesn't matter whether or not the clock protein has degraded because at that point it is invisible to the clock machinery.

"The circadian clock influences our daily lives in more ways than we can count," Dunlap says, "and this work points to how the clock might be manipulated to improve health."

More information: "Decoupling circadian clock protein turnover from circadian period determination" *Science*, www.sciencemag.org/lookup/doi/ … 1126/science.1257277

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