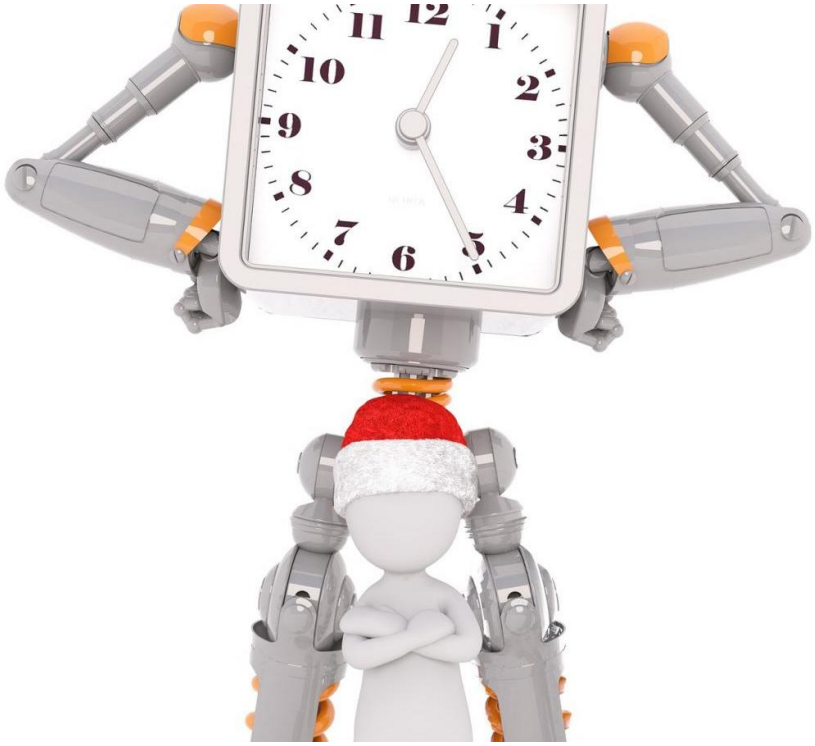
A key switch in biological clocks

May 29 2018



Credit: CC0 Public Domain

Just as we abide by an external time schedule to eat, sleep, and go to work, our body is similarly dictated by internal clocks. Known as circadian rhythms, these daily cycles keep us on a regular 24-hour day and are involved in numerous aspects of our well-being. When these biological clocks fail to work as they should, our bodies are out of phase with the outside world and this leads to many problems, not only sleep

disorders but obesity, cancer and mental health issues as well.

We have known about circadian rhythms for a long time, since 1729. We are learning a lot about how circadian rhythms work, and the 2017 Nobel prize for Medicine was awarded to circadian rhythms researchers.

Our circadian clocks can be misaligned by a variety of reasons. Some of us are morning larks, other night owls. Sometimes, mutations to our genes lead to the Familial Advanced Sleep Phase (FASP) condition. People with this mutation sleep and wake very early.

More worryingly, modern life is increasingly messing with our clocks. We stay awake at night with artificial lighting, often in front of glowing screens as we work late. In the morning, we are not awakened naturally but by alarm clocks. Such habits can override our natural circadian rhythms.

So how do these clocks work?

These clocks are intricately regulated by complex mechanisms, the details of which scientists are teasing out. We know that our molecular circadian clocks work via biochemical feedback loops with the aptly name PERIOD (PER) protein at the center. One process essential for molecular time keeping is a common process called phosphorylation.

Phosphorylation is the addition of a phosphate group, in this case to PER. Changes in phosphorylation of PER proteins due to mutations in can result in dramatic changes to circadian periods. But one large question was: what starts the phosphorylation of PER?

Previous research has suggested that a 'priming' kinase is required to 'switch on' the FASP site, a key control point that plays an important role in regulating our biological clock. However, despite much effort, the

identity of the priming kinase has yet to be discovered. Moreover, understanding of how phosphorylation of PER, a key control point, had been lacking until now.

An international team of researchers, led by Professor David Virshup in the Programme in Cancer and Stem Cell Biology, Duke-NUS Medical School, found that CK1 is the priming kinase.1 CK1 is a well-known kinase, though the discovery of this new key role is novel. The team also uncovered the mechanisms in which these proteins switch on the site. Members from the family of CK1 proteins cooperatively regulate the circadian clock. For example, while CK1D1 accelerates the circadian clock, CK1D2 slows it down.

By shining a light on this key part of how these CK1 proteins work on the circadian clock, we have a better understanding of what we can do when our circadian clock breaks down and problems arise, and the treatments we can develop. Those of us doing shift work or suffering from jet lag look forward to the day that drugs that inhibit CK1 allow us to wake and sleep on time!

More information: Rajesh Narasimamurthy et al, CK1δ/ε protein kinase primes the PER2 circadian phosphoswitch, *Proceedings of the National Academy of Sciences* (2018). DOI: 10.1073/pnas.1721076115

Provided by Duke-NUS Medical School

provided for information purposes only.