Keeping the body ticking: Scientists discover mechanism that regulates circadian clock

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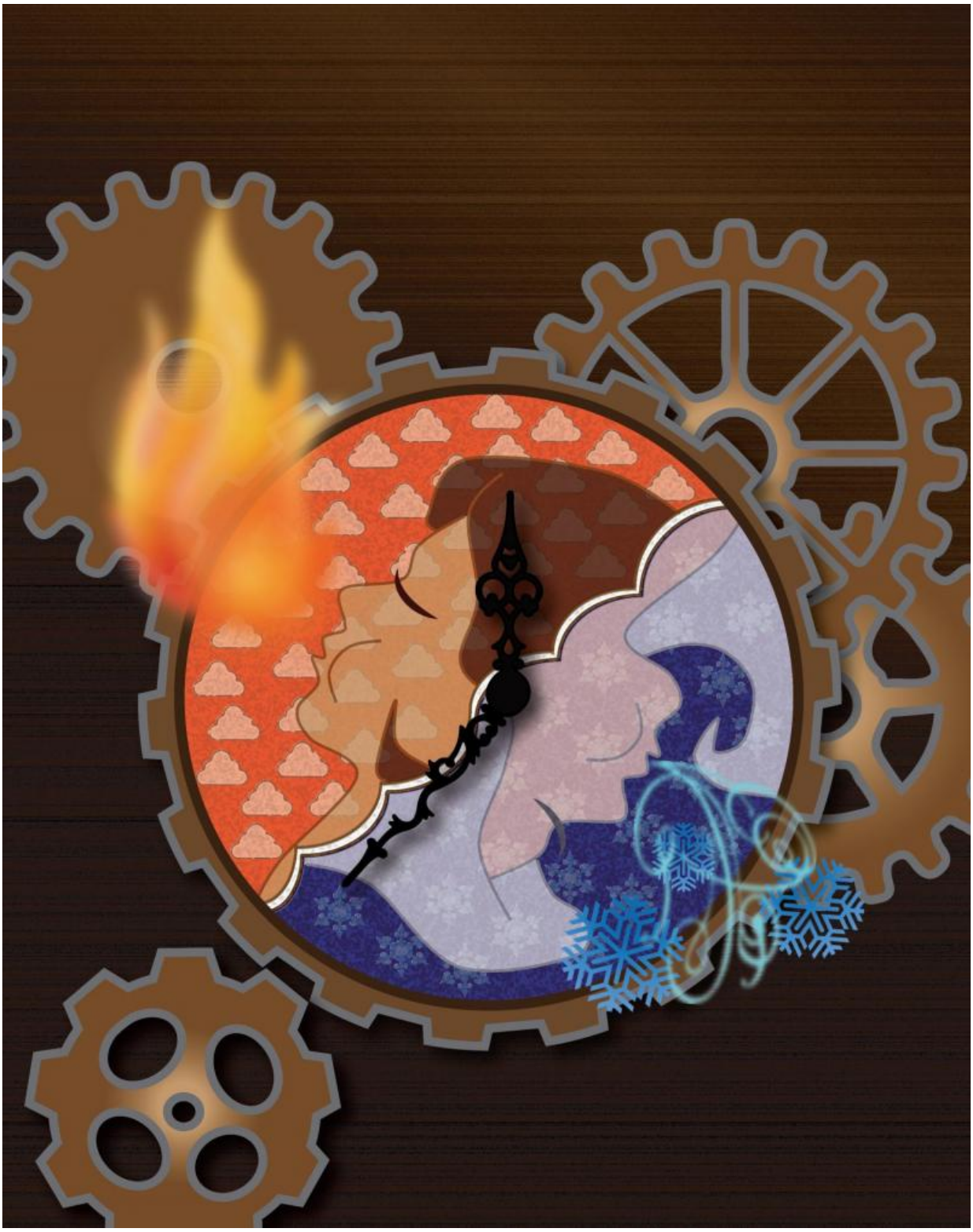

A temperature-sensitive switch regulates the body's circadian clock. Credit: Zhang Fuquan / Duke-NUS

Tick tock. Tick tock. A team of scientists from Duke-NUS Graduate Medical School Singapore (Duke-NUS) and the University of Michigan at Ann Arbor have discovered a molecular switch that regulates the body's circadian clock and allows it to keep time. This switch could be a potential drug target to treat circadian rhythm disorders caused by jet lag, shift work or metabolic disorders.

Normally, the circadian body clock (24-hour cycle) is synchronized with the rising and setting of the sun, ensuring that we sleep at night. One of the reasons this is possible is because the body clock is relatively insensitive to small changes in temperature. This is important because otherwise, the body clock could run too fast when it is hot or too slow when it is cold. A long-standing scientific mystery is how our body clock compensates for changes in temperature and maintains its speed.

Over the past few decades, research has advanced our understanding of the circadian clock. One of the proteins critical for determining the timing of the clock, as well as the timing of sleep, is Period2 (PER2).

In the current study, published 1 October 2015 in the journal *Molecular Cell* and led by Professor David Virshup from Duke-NUS and Professor Daniel Forger from Michigan, the findings shed light on how PER2 regulates our circadian clock. It also clarifies how the clock adapts to diverse conditions such as temperature and metabolic changes.

The research team found that the stability of PER2 is dependent on a process called phosphorylation, in which phosphates are added at key sites to influence the function of PER2. Dr Virshup and the team discovered that phosphorylation acts as a switch. This 'phosphoswitch' leads to two alternative fates for PER2: increased stability or increased degradation.

The researchers report that this phosphoswitch is sensitive to changes in temperature and metabolic signals and so it fine-tunes clock speed as needed. Usually, the rate of a biochemical reaction increases as the temperature rises, so in this case the speed of the body clock should increase if the temperature rises. However, the team showed that at higher temperatures, the phosphoswitch ensures that degradation of PER2 is slower, therefore maintaining the speed of the body clock.

"This study sheds light on one of the biggest mysteries of the circadian clock in the last 60 years and has helped to explain some of the basic mechanisms that govern the timing of the clock," explained Dr Virshup, Director of the Cancer and Stem Cell Biology Programme at Duke-NUS and Professor of Pediatrics at Duke University. "By using both biochemical analysis and mathematical modelling we demonstrated how the core circadian clock keeps to a 24-hour cycle despite temperature changes and metabolic changes."

The findings have several implications. The phosphoswitch gives researchers and scientists a potential drug target to influence the behaviour of the circadian clock. This new target may make it possible to counter the effects of jet lag, shift work and, perhaps, seasonal affective disorder.

The study also provides a mathematical model that accurately predicts the behaviour of the clock under different circumstances. This model will be useful in determining when drugs should be administered to modify circadian rhythms so that they are most effective.

The next step for the team is to test their predictions in an animal model. They plan to explore more about how phosphatases, an enzyme found in the body, and other kinases may be important in regulating the circadian clock. Their current hypothesis is that the interplay of these systems will regulate the sleep and wake cycle.

More information: Molecular Cell, Zhou and Kim et al.: "A Period2 Phosphoswitch Regulates and Temperature Compensates Circadian Period" dx.doi.org/10.1016/j.molcel.2015.08.022

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