Three genes essential for cells to tell time

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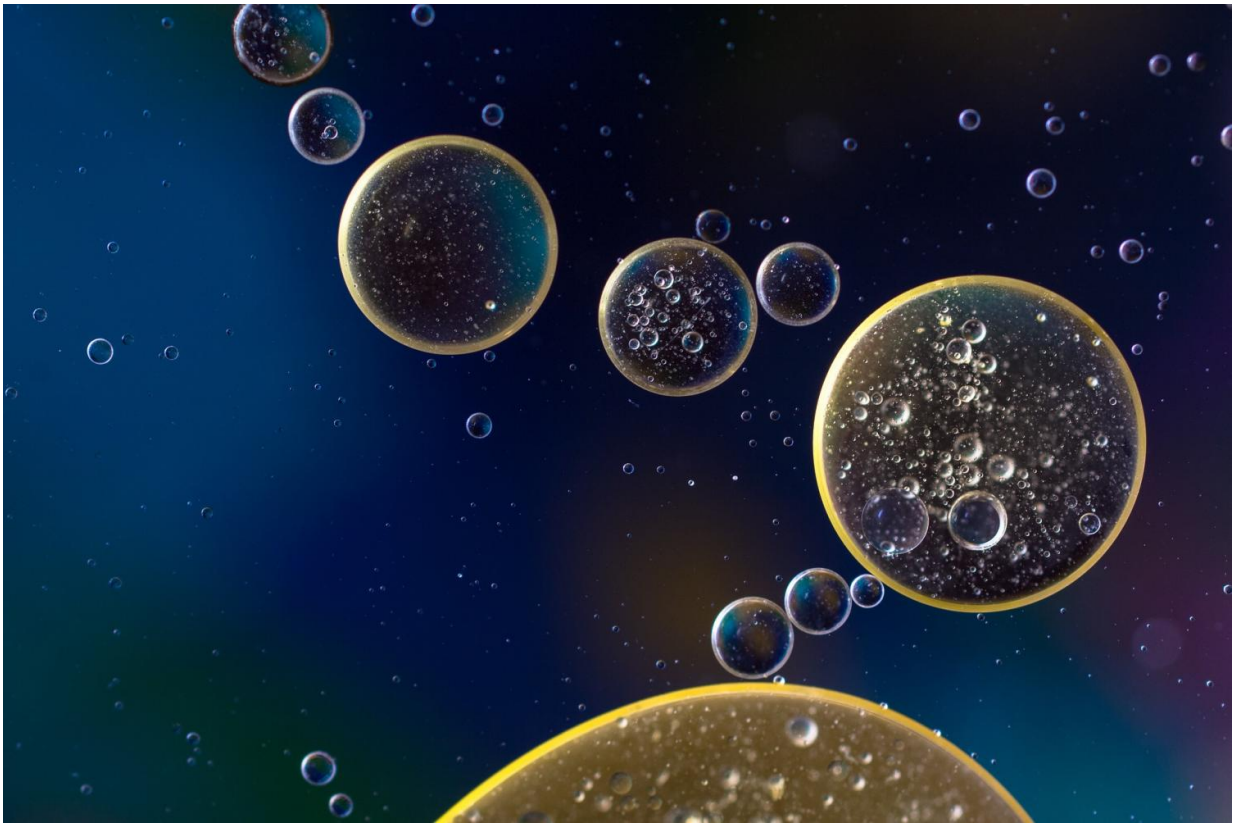

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One family of genes allows cells to adapt to daily changes in environmental conditions by adjusting the circadian clock responsible for regular sleep-wake cycles. The new discovery by University of Tokyo scientists reveals for the first time that circadian regulation may be directly connected to cellular stress.

Circadian rhythms are found in almost all organisms with sensitivity to light. Problems with circadian rhythms in humans are related to diseases including high blood pressure (hypertension), metabolic disorders and insomnia. Shift workers and the elderly have increased risk for these diseases as a result of disruption of their circadian clock.

The research team responsible for the work is based at the University of Tokyo and led by Professor Yoshitaka Fukada and Assistant Professor Hikari Yoshitane in the Department of Biological Sciences. The latest results stem from a series of ongoing experiments and continue to build on the lab's interests in circadian studies. Collaborators led by Professor Hidenori Ichijo of the Graduate School of Pharmaceutical Sciences developed the unique mice used in the experiments.

Researchers used cells and mice that lacked three genes: apoptosis signal-regulating kinase 1, 2, and 3 (Ask1, Ask2, Ask3). In results from both cells and mice, the Ask genes were necessary to respond to both sudden changes to the environment and gradual changes over time.

Cells without the Ask genes did not show the changes to their circadian rhythm that are expected from normal cells growing in environments with too high or too low salt or sugar concentrations. The cells without Ask genes were also impervious to the changes expected after cells accumulate too much oxidative stress. Uncontrolled oxidative stress creates potentially toxic environments within cells due to changes in chemical balance.

"Many researchers in this field have long suspected oxidative stress and circadian rhythms are somehow connected because of the cycles of photosynthesis and DNA replication we see even in ancient organisms; photosynthesis requires sunlight and creates free radicals that could damage DNA, so cells postpone DNA replication and cell division until nighttime when photosynthesis has stopped. We are very excited about

our results because we can approach the origin of the circadian clock by connecting oxidative stress and circadian regulation through the Ask genes," said Fukada.

The results in cells were further supported by observations of mouse behavior. Normal mice can change their wake-up time the next morning after unexpected light exposure during the night, as measured by their activity running on a wheel. Mice without Ask genes have less ability to synchronize their circadian clock to changes in environmental light-dark cycles.

"The dream is to have a tool to regulate circadian rhythms. Basic science like our research can show hints for later drug discovery work," said Yoshitane.

The University of Tokyo team plans to continue to study the detailed cellular mechanisms connecting Ask genes to oxidative stress and potential methods of influencing the circadian rhythm.

More information: ASK family kinases mediate cellular stress and redox signaling to circadian clock, *PNAS*, DOI: 10.1073/pnas.1719298115 , www.pnas.org/content/early/2018/03/16/1719298115

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