Study identifies 'master pacemaker' for biological clocks

March 27 2019

Mouse covering its eyes with its paw Credit: sibya via Pixabay

What makes a biological clock tick? According to a new study from U of T Mississauga, the surprising answer lies with a gene typically associated with stem and cancer cells.

In the first study of its kind for the field of circadian biology, UTM

researchers used RNAsequencing to observe the expression of genes in the suprachiasmatic nucleus (SCN), a tinyregion of the brain's hypothalamus region that governs the biological clock in mammals. Theirfindings pinpoint a gene that appears to regulate the biological clock and act as "master control"of the central circadian pacemaker.

Previously, the researchers were studying Period2, a gene found in the SCN, and were surprisedto observe that another gene known as SOX2 was also present in the same area. "We noticed thatPeriod2 was always expressed in the same population of cells as those that are expressed inSOX2—the biological clock was one of the major brain regions where these two genesoverlapped," says Hai-Ying Mary Cheng, associate professor with the Department of Biologyand Canada Research Chair in Molecular Genetics of Biological Clocks. "This is interestingbecause SOX2 is usually expressed in stem cells and in cancer cells, but we usually don't find itin large amounts in healthy adult brains or in neurons. We wondered if it might have a functionthat no one has previously thought about."

"Our research focuses on the basic understanding of how the biological clock organizes itself,"says lead author and Ph.D. candidate Arthur Cheng (no relation). He notes that events such asshift work, jet lag and travelling between time zones can disrupt circadian rhythms in humans."This can have a negative impact on health. Disrupted circadian rhythms are thought to beassociated with health issues like fatigue, cancers, heart attack and stroke."

Using mouse models that were missing the SOX2 gene, the researchers observed rodentbehaviour under controlled environmental conditions. "A normal mouse with a functioningbiological clock will start running on its wheel when the lights go off and will run through thenight," says Arthur Cheng. "They stop and go to bed when the lights come on, but when weknock out SOX2, the mice don't seem to know what they're doing."

"It's like their clock is broken or wonky," adds Hai-Ying Mary Cheng. "It's not telling timeproperly." The mice missing SOX2 also displayed weak running activity and irregular sleepingpatterns. "It was as if they were chronically jet-lagged," Arthur Cheng says, noting that the micealso had trouble adapting to new schedules. "They lost their rhythm, even with a smallmanipulation of light exposure," he says. "Adapting to jet-lag is built into our biologicalclocks—that's how we can survive intercontinental travel. But the mice missing the SOX2 genelost their ability to adapt."

"When we knocked out SOX2, we observed great changes in different gene networks in the SCNthat were very important to its neural network functions," says Hai-Ying Mary Cheng. "We thinkthat instead of regulating a single gene, SOX2 is coordinating the expression of many, manygenes, and contributing to the function of the SCN as the master regulator of the circadianpacemaker."

The study was published in the March 2019 issue of *Cell Reports*.

More information: Arthur H. Cheng et al, SOX2-Dependent Transcription in Clock Neurons Promotes the Robustness of the Central Circadian Pacemaker, *Cell Reports* (2019). DOI: 10.1016/j.celrep.2019.02.068

Provided by University of Toronto