Cellular thermometer discovered

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Scientists from Freie Universität Berlin have identified a mechanism that allows cells to adapt their gene expression program to very small changes in temperature. "Like a thermometer, these changes in gene expression follow the temperature in linear form and thus enable gradual adaptation to the given temperature," explains Prof. Dr. Florian Heyd from Freie Universität, who led the study. This cellular thermometer is sensitive enough to react to changes in body temperature between 36 and 38 ° C with altered gene expression. This discovery lays the foundation for a number of other, application-oriented questions. The experiments were carried out in mice, but since there are also time-of-the-day dependent differences in body temperature in humans, it is to be expected that the mechanism also plays an important role in human physiology. The findings were published in the highly regarded science journal *Molecular Cell*.

"The cells of warm-blooded organisms need a mainly constant temperature and tolerate deviations from the optimal 37 ° C only conditionally," explains Dr. Marco Preußner, who is a postdoctoral researcher and first author of the study. Even a change in temperature of +/- 5 ° C subjects the cell to a heat shock or cold shock, which can lead to cell death after a few hours. For this reason, warm-blooded animals must keep their body temperature relatively constant and prevent the body from adapting to the outside temperature. However, body temperature fluctuates slightly over the day: during the active phase (which for mice is in the dark because they are nocturnal animals), the body temperature is about 1.5 ° C higher than in the resting phase (in mice during the day).

The researchers in the RNA Biochemistry Group at Freie Universität Berlin were able to show that mice use this time-of-the-day-dependent change in body temperature to adapt gene expression to clock-dependent requirements. "This allows a large group of genes to be controlled rhythmically within a period of about 24 hours," Preußner said. The regulation is based on a process known as alternative splicing, through which the building blocks of the messenger RNA (mRNA) can be combined in different ways, which can lead to the formation of several protein variants from a single gene. "The alternative splicing of more than 100 genes reacts extremely sensitively to changes in temperature, so that different proteins are produced depending on the time of day and body temperature," said Prof. Dr. Florian Heyd. In addition, the total amount of a protein can be regulated by alternative splicing, which is illustrated in the current work by using the general transcription factor TBP (TATA-box binding protein) as an example.

In this case the temperature-dependent alternative splicing changes a non-coding region of the TBP mRNA, thereby regulating the efficiency with which the TBP protein is synthesized. This results in a clock-dependent oscillation of the TBP protein, possibly providing an explanation for the differences in the overall transcription rate, which scientists have known about for some time. "The mechanism we demonstrated is the most sensitive cellular thermometer known to date, since the signaling pathways that trigger a heat shock or cold shock hardly react in this physiologically relevant temperature range," explained Prof. Dr. Florian Heyd. On the basis of these findings, more application-oriented questions can now be investigated. Of particular interest is a possible association of temperature-dependent alternative splicing with the immune response during an infection with fever. As sensitive as alternative splicing reacts to (slightly) elevated temperature, a temperature-induced change in gene expression by fever appears to be a logical consequence. In further experiments the researchers plan to investigate the functionality of this mechanism in an infection.

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More information: Marco Preußner et al. Body Temperature Cycles Control Rhythmic Alternative Splicing in Mammals, *Molecular Cell* (2017). DOI: 10.1016/j.molcel.2017.06.006

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