Keeping the body in sync -- The stability of cellular clocks

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A study in Switzerland uses the tools of physics to show how our circadian clocks manage to keep accurate time in the noisy cellular environment.

In an article appearing March 13 in the journal *Molecular Systems Biology*, researchers from the Ecole Polytechnique Federale de Lausanne demonstrate that the stability of cellular oscillators depends on specific biochemical processes, reflecting recent association studies in families affected by advanced sleep phase syndrome.

Circadian rhythms are cyclical changes in physiology, gene expression, and behavior that run on a cycle of approximately one day, even in conditions of constant light or darkness. Peripheral organs in the body have their own cellular clocks that are reset on a daily basis by a central master clock in the brain. The operation of the cellular clocks is controlled by the coordinated action of a limited number of core clock genes. The oscillators work like this: the cell receives a signal from the master pacemaker in the hypothalamus, and then these clock genes respond by setting up concentration gradients that change in a periodic manner. The cell "interprets" these gradients and unleashes tissue-specific circadian responses. Some examples of output from these clocks are the daily rhythmic changes in body temperature, blood pressure, heart rate, concentrations of melatonin and glucocorticoids, urine production, acid secretion in the gastrointestinal tract, and changes in liver metabolism.

In the tiny volume of the cell, however, the chemical environment is constantly fluctuating. How is it possible for all these cell-autonomous clocks to sustain accurate 24-hour rhythms in such a noisy environment?

Using mouse fibroblast circadian bioluminescence recordings from the Schibler Lab at the University of Geneva, the researchers turned to dynamical systems theory and developed a mathematical model that identified the molecular parameters responsible for the stability of the cellular clocks. Stability is a measure of how fast the system reverts to its initial state after being perturbed.

“To my knowledge we are the first to discuss how the stability of the oscillator directly affects bioluminescence recordings,” explains Felix Naef, a systems biology professor at EPFL and the Swiss Institute for Experimental Cancer Research. “We found that the phosphorylation and transcription rates of a specific gene are key determinants of the stability of our internal body clocks.”

This result is consistent with recent research from the University of California, San Francisco involving families whose circadian clocks don’t tick quite right. These families’ clocks are shorter than 24 hours, and they also have mutations in oscillator-related genes. The current results shed light on how a genetically-linked phosphorylation event gone wrong could lead to inaccurate timing of our body clockworks.

Source: Ecole Polytechnique Fédérale de Lausanne