

The food-energy cellular connection revealed

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Our body's activity levels fall and rise to the beat of our internal drums—the 24-hour cycles that govern fundamental physiological functions, from sleeping and feeding patterns to the energy available to our cells. Whereas the master clock in the brain is set by light, the pacemakers in peripheral organs are set by food availability. The underlying molecular mechanism was unknown.

Now, researchers at the Salk Institute for Biological Studies shed light on the long missing connection: A metabolic master switch, which, when thrown, allows nutrients to directly alter the rhythm of peripheral clocks.

Since the body's circadian rhythm and its metabolism are closely intertwined, the risk for metabolic disease shoots up, when they are out of sync. "Shift workers face a 100 percent increase in the risk for obesity and its consequences, such as high blood pressure, insulin resistance and an increased risk of heart attacks," says Howard Hughes Medical Investigator Ronald M. Evans, Ph.D., a professor in the Salk Institute's Gene Expression Laboratory.

The researchers' findings, which are published in the Oct. 16, 2009, issue of *Science*, could have far-reaching implications, from providing a better understanding how nutrition and gene expression are linked, to creating new ways to treat obesity, diabetes and other related diseases. "It is estimated that the activity of up to 15 percent of our genes is under the direct control of biological clocks," says Evans. "Our work provides a conceptual way to link nutrition and energy regulation to the genome."

The clocks themselves keep time through the rhythmic waxing and waning of circadian [gene expression](#) on a roughly 24-hour schedule that anticipates environmental changes and adapts many of the body's physiological functions to the appropriate time of day. The most obvious one, the sleep-wake rhythm, is tightly linked to the night-day cycle. But so are physical activity and metabolism.

"When we get up in the morning we 'break the fast'," says Evans. While opening the fridge doesn't require a lot of physical activity, the situation for animals in the wild is quite different. "If you are a predatory animal you run to hunt. If you are prey, you run to get away."

But how pacemakers in peripheral tissues such as the liver and muscle knew that it was time to scurry and replenish their energy stores was still an open question. When postdoctoral researcher and first author Katja Lamia, Ph.D., started probing the relationship between metabolism and circadian cycles, she discovered a highly conserved phosphorylation site in CRY1, short for cryptochrome 1. Cryptochromes originally evolved as a blue light photoreceptor in plants and, although no longer sensitive to light, are now an integral part of the clock in vertebrates.

The phosphorylation site is specific for AMPK, which acts like a gas gauge by sensing how much energy a cell has. When a cell has plenty of energy, AMPK remains inactive and the cell carries out its normal processes. Her experiments revealed that if a cell runs on empty, AMPK is turned on and attaches a phosphate molecule to CRY1, which initiates the destruction of CRY1. As a result the circadian rhythm speeds up and the clock is reset.

"The insertion of an AMPK phosphorylation site transformed a light sensor into an energy sensor, which now allows nutrients to provide metabolic input to circadian clocks," explain Lamia. "Insertion of a novel sensor into an existing signaling pathway is a very elegant solution

to a rather complicated problem."

Genetic inactivation of AMPK in mice blocks these effects, stabilizing CRY1 and severely disrupting peripheral clocks. In contrast, treating mice with AICAR, a synthetic drug that directly activates AMPK, reset the clock in cultured cells as well as in animals, confirming that cryptochromes act as energy sensors that allow to circadian clocks.

Source: Salk Institute ([news](#) : [web](#))

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