

At the heart of the circadian clock

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Credit: Ana Blazic Pavlovic / fotolia.com

(Phys.org) —Cellular processes in most organisms are regulated by an internal clock, and proteins called cryptochromes are at the core of its central oscillator. The three dimensional structures of cryptochromes from mouse and fruitfly have now been determined.

Many biological processes, from gene expression programs to the secretion of hormones and the operation of the immune system, proceed in rhythmic patterns that are determined by a [molecular clock](#), a central oscillator that is coupled to the circadian light-dark cycle. Proteins called cryptochromes are a crucial component of the clock mechanism. In mammals, cryptochromes are critically involved in the control of diurnally regulated [biochemical processes](#) – including [glucose metabolism](#). Unlike its counterparts in mammals, the sole [cryptochrome](#)

in the fruitfly *Drosophila* is sensitive to blue light and helps to synchronize the internal oscillator with the daily photoperiod.

Researchers have long sought to determine the [three-dimensional structures](#) of the two mammalian cryptochromes (mCRY1/2) and the sole cryptochrome in *Drosophila* (dCRY). "Only high-resolution structures can provide the information we need to work out in detail how mCRY regulates the [biological clock](#) and understand the precise mode of action of dCRY," says Privatdozent Dr. Eva Wolf of LMU's Adolf Butenandt Institute, who led the team that has successfully used X-ray crystallography to define the structures of the fruitfly cryptochrome and mammalian cryptochrome 1.

CRYs set the clock's period

The structures provide fundamentally new insights into the [molecular mechanisms](#) that control the clock period set by the central oscillator. For example, it emerges that synchronization of the *Drosophila* clock by blue light is mediated by a previously unknown phototransduction mechanism that results in light-induced changes in the spatial conformation of dCRY.

"The structural analysis of mCRY1 has revealed how this cryptochrome interacts with other components of the biological clock. These interactions regulate the stability of mCRY1 – and this determines the oscillation period of the clock," says Wolf. Other regions of mCRY1 bind to a transcription factor and prevent it from activating genes involved in a range of periodic physiological processes and behaviors, ensuring that these are triggered and repressed with a circadian rhythm.

Keeping time keeps one healthy

The control of physiology by the biological clock also has implications for health. Thus persons whose lifestyles conflict with their inner timekeeper not only suffer from sleep disturbances, but are at increased risk for more serious disorders. "Shiftworkers are more likely to get cancer or develop metabolic syndrome," says Wolf. For instance, mCRYs play a role in the regulation of glucose levels – and perturbation of this control circuit can lead to metabolic disorders including Type-2 diabetes. "Our findings may open up new ways of treating these conditions by facilitating the design of drugs that target cryptochrome function," Wolf concludes.

More information: *Cell* 2013:

[www.cell.com/abstract/S0092-8674\(13\)00576-X](http://www.cell.com/abstract/S0092-8674(13)00576-X)

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