Scientists identify new mechanism regulating daily biological rhythms

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Scientists from the Florida campus of The Scripps Research Institute have identified for the first time a novel mechanism that regulates circadian rhythm, the master clock that controls the body's natural 24-hour physiological cycle. These new findings could provide a new target not only for jet lag, shift work, and sleep disturbances, but also for disorders that result from circadian rhythm disruption, including diabetes and obesity as well as some types of cancer.

The study is published in the November 12, 2010 edition (Volume 285, Number 45) of the Journal of Biological Chemistry.

"It's well known that the nuclear receptors RORα and REV-ERBα regulate expression of the gene BMAL1, which is vital to virtually every aspect of human physiology and a core component of the circadian clock ," said Tom Burris, a professor in the Department of Molecular Therapeutics at Scripps Florida who led the study. "BMAL1 functions as an obligate heterodimer (only working as a dimer with a partner) with either CLOCK or NPAS2 so it was unclear how RORa and REV-ERBa could control this complex. In this study, we show that both partners are targets. As we understand more about the relationship between these receptors and their gene targets, we can consider the possibility of modulating the body's core clock, especially as we continue to develop synthetic ligands targeting these two nuclear receptors."

Circadian rhythms are conserved across a wide variety of organisms, from *Drosophila* (fruit flies) to humans. In mammals, these rhythms

respond to light signals and are controlled by the "master clock" in the brain. In the periphery, semi-autonomous clocks can respond to signals from the brain and from other cues including nutrient status. Disorders linked to dysfunctional circadian rhythms can be severe and potentially deadly, Burris said.

"When you're dealing with circadian rhythm, the most obvious disease target is sleep – for people who do shift work, critical jobs like police work, fire fighting, and medicine," he said. "If circadian rhythm is disrupted, you're prone to metabolic disorders like diabetes and obesity and even breast cancer – because the core clock is closely linked to the cell cycle. If your clock goes awry, you run the risk of your cell cycle going awry as well."

The Role of Nuclear Receptors

Nuclear receptors are proteins that recognize and regulate hormones as well as other molecules. As a result, they control an organism's metabolism by activating gene expression.

The study found that oscillations in the expression of RORα and REV-ERBα not only influence the pattern of circadian expression of BMAL1, but also of NPAS2, a protein that is part of the circadian clock. The fact that NPAS2 is a target of both receptors suggests that there is a specific mechanism that coordinates the relative levels of each receptor to maintain correct circadian function..

"Based on the fact that BMAL1 and NPAS2 work together within the circadian clock, it seems highly unlikely that these two nuclear receptors would only regulate one of them," Burris said. "Our study shows for the first time that, like BMAL1, NPAS2 is also a direct target for RORα and REV-ERBα. This discovery makes this complex a very good therapeutic target."

The expression of RORα and REV-ERBα follows a 24-hour circadian pattern (with opposing phases) leading to the correct circadian pattern of gene expression of BMAL1 and NPAS2.

"We think it's something of a competition between these two receptors for binding to promoters of these genes that triggers either the activation (RORα) or repression (REV-ERBα) of the gene," Burris said.

Nuclear receptors make tempting drug targets because they can bind directly to DNA and activate genes through specific ligands—molecules that affect receptor behavior—such as the sex hormones, vitamins A and D, and glucocorticoids, which modulate the body's response to stress. Nuclear receptors have been implicated in a number of cancers, including prostate, breast, and colon cancers, and other diseases as well, including type 2 diabetes, atherosclerosis, and metabolic syndrome.

The other important aspect of nuclear receptors is their practicality. Scientists can design small molecule therapeutics to force them to change their ways. Burris said that he has already identified several new synthetic ligands (drug like molecules) for both receptors.

More information: The first author of the study, "Characterization of the Core Mammalian Clock Component, NPAS2, as a REV-ERBα/RORα Target Gene," is Christine Crumbley of The Scripps Research Institute. www.jbc.org/content/285/46/35386.abstract

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