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Coordinating the circadian clock: Researchers find that molecular pair controls time-keeping and fat metabolism

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(PhysOrg.com) -- The 24-hour internal clock controls many aspects of human behavior and physiology, including sleep, blood pressure, and metabolism. Disruption in circadian rhythms leads to increased incidence of many diseases, including metabolic disease and cancer. Each cell of the body has its own internal timing mechanism, which is controlled by proteins that keep one another in check.

One of these proteins, called Rev-erb alpha, was thought to have a subordinate role because the clock runs fairly normally in its absence. New work, published in Genes and Development this month, from the lab of Mitchell Lazar, MD, PhD, director of the Institute for Diabetes, Obesity, and Metabolism at the Perelman School of Medicine, University of Pennsylvania, found that a closely related protein called Rev-erb beta serves as a back-up for Rev-erb alpha. When both are not functioning, the cellular clock loses its time-keeping function.

The two Rev-erbs work together to control fat metabolism, and in their absence, the liver fills with fat. These findings establish the Rev-erbs as major regulators of both clock function and metabolism.

Lazar, postdoctoral fellow Anne Bugge, PhD, and the team knocked out Rev-erb alpha in mice and didn't see a large effect on the liver. When they knocked out both Rev-erb alpha and Rev-erb beta, they saw a loss of the rhythmic cycling of the clock protein Bmal 1's messenger RNA.

They concluded that the Rev-erb system is an integral part of the human clock, not ancillary.

Prior to this paper, the Lazar team discovered molecules that act as "shift workers" to maintain the daily rhythm of fat metabolism. When those molecules do not do their jobs, the liver also dramatically fills with fat.

In normal mice, the team of molecules migrates to the genome of liver cells during the daytime. Rev-erb, one of the team members, delivers the molecular workers to thousands of specific locations in the liver genome, many of which are near genes involved in the production of fat. Another team member, histone deacetylase 3 (HDAC3), does construction work on the protein scaffold (the epigenome) surrounding the genome to dampen the activity of the fat-related genes.

During the night, the day shift molecules depart the liver genome, and fat production increases due to other regulatory molecules. The fat production is kept in check when the Rev-erb construction team returns to the genome the next day. However, if HDAC3 is absent, the cycles do not occur, and the liver fills with fat.

The absence of both Rev-erbs prevents HDAC3 from doing its job, since Rev-erbs serve as the shuttle delivering HDAC3 to target genes. Sure enough, fat accumulates in the liver to a much great extent when both Rev-erbs are missing compared to when one is still available.

"This work shows that if we want to manipulate the human clock we would likely need to affect both Rev-erb alpha and Rev-erb beta," explains Lazar. "Circadian rhythm of metabolism is important because disruption of this rhythm leads to a fatty liver. This may explain, in part, why altered circadian rhythms in people who do shift work is associated with metabolic disorders."