Circadian rhythms can be modified for potential treatment of disorders

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(Medical Xpress)—UC Irvine-led studies have revealed the cellular mechanism by which circadian rhythms – also known as the body clock – modify energy metabolism and also have identified novel compounds that control this action. The findings point to potential treatments for disorders triggered by circadian rhythm dysfunction, ranging from insomnia and obesity to diabetes and cancer.

UC Irvine's Paolo Sassone-Corsi, one of the world's leading researchers on the genetics of circadian rhythms, led the studies and worked with international groups of scientists. Their results are detailed in two companion pieces appearing this week in the early online edition of the Proceedings of the National Academy of Sciences.

"Circadian rhythms of 24 hours govern fundamental physiological functions in almost all organisms," said Sassone-Corsi, the Donald Bren Professor of Biological Chemistry. "The circadian clocks are intrinsic time-tracking systems in our bodies that anticipate environmental changes and adapt themselves to the appropriate time of day. Disruption of these rhythms can profoundly influence human health."

He added that up to 15 percent of people's genes are regulated by the day-night pattern of circadian rhythms.

In one study, Sassone-Corsi and colleagues found that the biological clock controls enzymes localized in the mitochondrion, a cellular structure devoted to energy metabolism. This government occurs through

acetylation of proteins, a process that operates as a switch to turn genes on and off in cells based upon the cells' energy usage.

Some of the most important acetylation events in cells are dictated by an enzyme protein called SIRT1, which senses energy levels in the cell. Its activity is modulated by how many nutrients a cell is consuming. It also helps cells resist oxidative and radiation-induced stress. SIRT1 has been linked to the inflammatory response, diabetes and aging.

Sassone-Corsi first showed the circadian rhythm-metabolism link in 2008 and 2009, and in this study, he and his colleagues reveal the metabolic pathways through which SIRT1 works.

"When the balance between clock proteins is upset, normal cellular function can be disrupted," said Sassone-Corsi, who also directs the Center for Epigenetics & Metabolism at UC Irvine.

In exploring how to regulate SIRT1 activity, Sassone-Corsi teamed with scientists from two research-and-development groups at GlaxoSmithKline – one in the United Kingdom and the other (called Sirtris) in the U.S. – to test proprietary small-molecule compounds that stimulate SIRT1.

In mouse studies, they were able to modulate the scale of circadian-driven gene function with the SIRT1-activating compounds, effectively governing the circadian cycle in a host of genes involved with the metabolic rate in cells. This research proves that small molecules can be used as a pharmacological strategy to control circadian disturbances and is a step toward the development of drugs that could target many conditions, including metabolic disorders, diabetes, cancer and aging.

Postdoctoral researchers Selma Masri and Kristin Eckel-Mahan, graduate student Vishal Patel and Chancellor's Professor Pierre Baldi of

UC Irvine, along with Shahaf Peleg, Ignasi Forne, Andreas Ladurner and Axel Imhof of Germany's University of Munich, as well as Sassone-Corsi, contributed to the study titled "The Circadian acetylome reveals regulation of mitochondrial metabolic pathways." The National Institutes of Health, the National Science Foundation, INSERM and Sirtris provided support.

In addition to Sassone-Corsi, postdoctoral researcher Marina Bellet and laboratory assistant Marlene Cervantes of UC Irvine; Mohamed Boudjelal, Emma Watts, Danuta Mossakowska and Kenneth Edwards of GlaxoSmithKline; Giuseppe Astarita of Georgetown University; and Christine Loh, James Ellis and George Vlasuk of Sirtris contributed to the study titled "Pharmacological modulation of circadian rhythms by high-affinity SIRT1 activators." The National Institutes of Health and INSERM provided support.

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