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Strict genomic partitioning by biological clock separates key metabolic functions

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Much of the liver's metabolic function is governed by circadian rhythms – our own body clock – and UC Irvine researchers have now found two independent mechanisms by which this occurs.

The study, published online today in *Cell*, reveals new information about the body clock's sway over metabolism and points the way to more focused drug treatments for liver disease and such metabolic disorders as obesity and diabetes.

Paolo Sassone-Corsi, UCI's Donald Bren Professor of Biological Chemistry, and postdoctoral scholar Selma Masri report that two of these circadian-linked proteins, SIRT1 and SIRT6, manage important liver processes – lipid storage and energy usage in liver cells – separately and distinctly from each other.

This surprising discovery of genomic partitioning, Masri noted, reveals how strictly regulated circadian control of metabolism can be.

"The ability of the genome and epigenome to cross-talk with metabolic pathways is critical for cellular and organismal functions. What's remarkable is that the circadian clock is intimately involved in this dialogue," she said.

Circadian rhythms of 24 hours govern fundamental physiological functions in virtually all organisms. The circadian clocks are intrinsic time-tracking systems in our bodies that anticipate environmental

changes and adapt themselves to the appropriate time of day. Changes to these rhythms can profoundly influence human health. Up to 15 percent of people's genes are regulated by the day-night pattern of circadian rhythms; nearly 50 percent of those involved with metabolic pathways in the liver are influenced by these rhythms.

SIRT1 and SIRT6 belong to a group of proteins called sirtuins that participate in epigenetic control of the genome and help regulate important biological processes ranging from cell health maintenance to lipid storage and energy expenditure in cells. They're widely studied for their effect on metabolism and longevity.

To discover how SIRT1 and SIRT6 work independently of each other, Masri and Sassone-Corsi conducted tests with two sets of mice – one with SIRT1 in the liver knocked out and the other with SIRT6 nullified.

The two sirtuins, the scientists learned, are committed to the control of distinct genomic domains, with hundreds of genes being SIRT1-dependent and hundreds of others relying on SIRT6. This resulted in a distinct partition of metabolic pathways and physiological functions, Sassone-Corsi said.

He added that these findings pave the way to further investigations that may facilitate the design of pharmacological strategies targeting SIRT1- or SIRT6-specific metabolic functions and pathologies.

Provided by University of California, Irvine