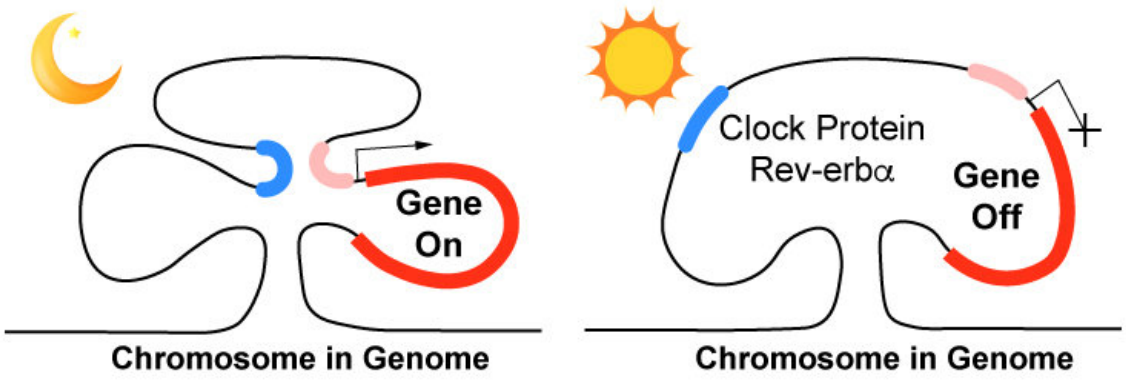
Clock protein controls daily cycle of gene expression by regulating chromosome loops

February 9 2018, by Karen Kreeger



Schematic of Rev-erb's role in gene expression. At night (left), when Rev-erb concentration decreases, gene expression is turned on by protein complexes that loop the chromosome bringing together distant regions (blue and pink). During the day (right), when Rev-erb levels rise, the protein complexes are kicked out, causing the loop to loosen and turn off gene expression. Credit: Yong Kim and Mitch Lazar, Perelman School of Medicine, University of Pennsylvania

It's well known that the human body functions on a 24-hour, or circadian, schedule. The up-and-down daily cycles of a long-studied clock protein called Rev-erb coordinates the ebb and flow of gene expression by tightening and loosening loops in chromosomes, according to new research from the Perelman School of Medicine at the University of Pennsylvania. The findings appear online this week in *Science*.

Over the last 15-plus years, a team led by the new study's senior author Mitchell A. Lazar, MD, Ph.D., director of Penn's Institute for Diabetes, Obesity, and Metabolism, has been teasing out the versatile role of Rev-erb in maintaining daily cycles of the body's molecular clock, metabolism, and even brain health.

"Many studies, including this one, point to a link between the human internal clock and such metabolic disorders as obesity and diabetes," Lazar said. "Proteins such as Rev-erb are the gears of the clock and understanding their role is important for investigating these and many other diseases."

Human physiology works on a 24-hour cycle of gene expression (when the chromosome coding region is translated by RNA and then transcribed to make protein) and is controlled by the body's molecular clock. Core clock proteins activate or repress protein complexes that physically loop one part of a chromosome to become adjacent to a distant part of the same chromosome.

The Penn team showed that daily oscillations of Rev-erb control gene expression in the mouse liver via interactions between on-and-off regions on the same chromosome. Previous work from the team demonstrated that by 5 p.m., Rev-erb increases to its highest concentration in mouse liver, where it turns off certain genes and therefore protein transcription. But as the day turns to night, its concentration steadily decreases and nearly vanishes from the liver by 5

a.m.

Without Rev-erb around, expression of its target genes returns. And this process repeats normally, day after day. Other researchers have established that activator proteins drive the formation of chromosome loops to turn on genes; however, how repressor proteins such as Rev-erb regulate their part in turning off gene expression has remained unanswered, until now.

In this study, the team demonstrated that Rev-erb represses transcription by loosening chromosome loops. Rev-erb kicks out the protein complexes that bridge the distant regions of the chromosome, thereby destabilizing the loop and turning off the gene.

"The mechanisms by which Rev-erb loosens loops in DNA, leading to circadian repression of transcription, are likely to apply to other clock proteins," Lazar said. Recent studies have tied Rev-erb to cancer and cardiovascular disease. The team aims to look at new drugs that affect chromosome looping to see how it may affect gene expression in cancer cells and tissues other than the liver.

More information: Yong Hoon Kim et al. Rev-erbα dynamically modulates chromatin looping to control circadian gene transcription, *Science* (2018). DOI: 10.1126/science.aao6891 , science.sciencemag.org/content … 2/07/science.aao6891

Provided by University of Pennsylvania

Citation: Clock protein controls daily cycle of gene expression by regulating chromosome loops (2018, February 9) retrieved 25 April 2024 from https://medicalxpress.com/news/2018-02-clock-protein-daily-gene-chromosome.html

This document is subject to copyright. Apart from any fair dealing for the purpose of private study or research, no part may be reproduced without the written permission. The content is provided for information purposes only.