CIRCADIAN GENETICS

Central government versus local control

A fundamental change in our understanding of mammalian circadian biology came with the realization that the mechanisms that drive daily rhythms are present not only in a master pacemaker in the brain, but also in most cells throughout the body. This means that circadian gene expression in peripheral tissues might be under the control of either local clocks or systemic circadian cues that are driven by the master pacemaker. A new study reveals that in fact both forms of control are important.

To investigate the 'power-sharing' between central and local clocks, Kornmann and colleagues devised a method to inactivate the clock mechanism specifically in mouse liver cells.

The transcription factor BMAL1 (also known as ARNTL) is an essential component of the mammalian oscillator — the molecular mechanism that

drives circadian rhythmicity — and is negatively controlled by another protein, REV-ERB α (also known as NR1D1). The authors generated transgenic mice in which *Rev-erba* is expressed in the liver only, under the control of tetracycline-responsive elements. So, the expression of BMAL1 could be turned on or off through *Rev-erba* expression in a tightly controlled way using dietary supplements.

Kornmann and colleagues used microarray hybridization to assess alterations in genome-wide expression patterns when BMAL1 expression is repressed in the liver. For most transcripts that usually show a circadian expression pattern, normal cycling was altered when BMAL1 levels were low, indicating their dependence on the functioning of the local oscillator in the liver. However, a smaller subset of transcripts that fall into this class were unaffected by the downregulation of BMAL1 expression. These are good candidates for genes whose circadian regulation is controlled by systemic cues.

Intriguingly, one of the genes that fell into this latter category was period homologue 2 (*Per2*), another key component of the oscillator mechanism — a surprising finding as *Per2* is transcriptionally activated by BMAL1. The authors investigated the relative contributions of these two modes of *Per2* regulation by monitoring the expression of this gene

in cultured liver explants — where systemic signals cannot operate. In liver explants from mice in which BMAL1 is downregulated, circadian *Per2* expression was abolished. So, it seems that *Per2* expression can be driven by local clocks in the liver as well as by systemic cues.

This study provides several new insights into mammalian circadian biology. First, local oscillators and systemic cues both seem to regulate circadian patterns of gene expression in peripheral tissues. Second, the fact that an oscillator component, PER2, can be regulated independently of the local clock mechanisms makes it a potential point for synchronization of local oscillators by the central pacemaker. Kornmann and colleagues already have evidence that PER2 expression is temperature dependent. Exploring the roles of body temperature and other potential systemic cues that regulate circadian expression in peripheral tissues will be an important next step.

Louisa Flintoft

ORIGINAL RESEARCH PAPER

Kornmann, B. *et al.* System-driven and oscillator-dependent circadian transcription in mice with a conditionally active liver clock. *PLoS Biol.* 5, e34 (2007)

FURTHER READING Bell-Pedersen, D. *et al.* Circadian rhythms from multiple oscillators: lessons with diverse organisms. *Nature Rev. Genet.* 6, 544–556 (2005)

WEB SITE

Ueli Schibler's web site:
<http://www.molbio.unige.ch/schibler/index.php>

RESEARCH HIGHLIGHTS ADVISORS

MICHAEL AKAM
University of Cambridge, UK
SEAN B. CARROLL
University of Wisconsin, USA
NANCY J. COX
University of Chicago, USA
SUSAN FORSBURG University of Southern California, USA

RALPH J. GREENSPAN
The Neurosciences Institute, California, USA
YOSHIHIDE HAYASHIZAKI
Riken Genomic Sciences Center, Japan
MARK JOBLING
University of Leicester, UK

PETER KOOPMAN
University of Queensland, Australia
LEONID KRUGLYAK
Fred Hutchinson Cancer Research Center, USA
BARBARA MEYER
University of California, Berkeley, USA

JOHN QUAKENBUSH
Dana-Farber Cancer Institute and Harvard School of Public Health, Boston, USA
JANET ROSSANT
Mount Sinai Hospital, Toronto, Canada
MARC VIDAL Dana-Farber Cancer Institute, Boston, USA

VIRGINIA WALBOT
Stanford University, USA
DETLEF WEIGEL Max Planck Institute for Developmental Biology, Germany
PHIL ZAMORE
University of Massachusetts, USA
LEONARD I. ZON
Children's Hospital, Boston, USA