Mathematical models converge on PGC1α as the key metabolic integrator of SIRT1 and AMPK regulation of the circadian clock

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How the mammalian circadian clock interacts with metabolism and its possible implications in metabolic diseases are actively studied. In PNAS, Foteinou et al. (1) propose a mathematical model of the circadian clock that incorporates the metabolic sensor SIRT1 and validate it with cell experiments. Their findings shed light on conflicting reports by Asher et al. (2) and Nakahata et al. (3) about the effect of *SIRT1* deficiency on clock function and SIRT1 targets. The authors conclude that SIRT1 acts on the clock not only via the well-known clock protein PER2, but also through PGC-1α, a transcriptional co-activator of the BMAL1 clock gene with key metabolic functions.

Interestingly, the Foteinou model is comparable to the model designed by Woller et al. (4) to understand the mechanisms of liver clock disruption observed upon high-fat diet (HFD) consumption. The two models describe the dynamics of the same molecular network, except that Woller et al. additionally consider clock regulation by the energy sensor AMPK. Remarkably, both models point to a key role of PGC-1α in the circadian clock from different perspectives. The Woller model takes into account the NAMPT-NAD+-SIRT1-PGC1α-ROR-BMAL1 metabolic loop and show its requirement to reproduce the dampened oscillations in clock gene expression observed by Hatori et al. (5) and Eckel-Mahan et al. (6) upon HFD feeding, a condition mimicked by altered AMPK activity. On the other hand, Foteinou et al. (1) report that inclusion of PGC-1α in their model is needed to reproduce correctly the altered reporter expression levels upon combined *SIRT1* and *BMAL1* silencing. These findings confirm the role of PGC-1α linking SIRT1 and AMPK activities: PGC-1α needs to be phosphorylated by AMPK before it can be deacetylated by SIRT1 (7). The key role of PGC-1α,

highlighted by both the Foteinou and Woller models, is all the more notable given that these two models do not agree on all interactions between metabolism and the clock. For example, removing deacetylation of PER2 by SIRT1 in the Woller model does not diminish its precise adjustment to expression data from mouse livers obtained by different genetic modifications (WT, SIRT1 KO, LKB1 KO). This may be due to differences in the studied models (liver tissue vs cell lines). Still, both studies pinpoint the usefulness of mathematical models to decipher and predict key components in signaling circuits and their mechanistic implication.

In conclusion, PGC-1α has long been known as an important physiological player, notably associated with mitochondrial biogenesis and fatty-acid oxidation (8). Its role in the circadian clock, first reported by Liu et al. (9), is emphasized by two recent data-driven modeling studies addressing different questions in different models (1,4). Given that PGC-1α integrates signals from NAD+ (via SIRT1) and AMP (via AMPK) (10), two key metabolites associated with several biochemical reactions consuming or producing energy, these findings provide further confirm the tight link between the circadian clock and metabolism. Advancing our understanding of this interaction is needed to assess the role of the circadian clock in metabolic diseases such as obesity and type-2 diabetes.

References

(1) P.T. Foteinou et al., « Computational and experimental insights into the circadian effects of SIRT1 », Proc. Natl. Acad. Sci. 115, 11643–11648 (2018).
(2) G. Asher et al., « SIRT1 regulates circadian clock gene expression through PER2 deacetylation », Cell 134, 317-328 (2008).
(3) Y. Nakahata et al., « The NAD+-dependent deacetylase SIRT1 modulates CLOCK-mediated chromatin remodeling and circadian control », Cell 134, 329-340 (2008).
(4) A. Woller et al., « A Mathematical Model of the Liver Circadian Clock Linking Feeding and Fasting Cycles to Clock Function. », Cell Rep. 17, 1087-1097 (2016).
(5) M. Hatori et al., « Time-restricted feeding without reducing caloric intake prevents metabolic diseases in mice fed a high-fat diet », Cell Metab. 15, 848-860 (2012).
(6) K.L. Eckel-Mahan et al., « Reprogramming of the circadian clock by nutritional challenge », Cell 155, 1464-1478 (2013).
(7) C. Cantò et al., « Interdependence of AMPK and SIRT1 for metabolic adaptation to fasting and exercise in skeletal muscle", Cell Metab. 11, 213-219 (2010)

(8) J. Lin, C. Handschin and B. Spiegelman, « Metabolic control through the PGC-1 family of transcription activators », Cell Metab. 1, 361-370 (2005).
(9) C. Liu et al., « Transcriptional coactivator PGC-1alpha integrates the mammalian clock and energy metabolism », Nature 447, 477-81 (2007).
(10) C. Cantò and J. Auwerx, « PGC-1alpha, SIRT1 and AMPK, an energy-sensing network that controls energy expenditure », Curr. Opin. Lipidol. 20, 98-105 (2009).