Mathematical models converge on PGC1 α 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. Foteinou et al. (1) conclude that SIRT1 acts on the clock not only via the well-known clock protein PER2, but also through PGC1 α , a transcriptional coactivator of the BMAL1 clock gene with key metabolic functions.

Interestingly, the Foteinou et al. (1) 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 2 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 PGC1 α in the circadian clock from different perspectives. The Woller et al. (4) model takes into account the NAMPT-NAD⁺-SIRT1-PGC1 α -ROR-BMAL1 metabolic loop and shows 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 PGC1 α 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 PGC1 α linking SIRT1 and AMPK activities: PGC1 α needs to be phosphorylated by AMPK before it can be deacetylated by SIRT1 (7). The key role of PGC1 α , highlighted by both the Foteinou et al. and Woller et al. models, is all the more notable given that these 2 models do not agree on all interactions between metabolism and the clock. For example, removing deacetylation of PER2 by SIRT1 in the Woller et al. model does not diminish its precise adjustment to expression data from mouse livers obtained by different genetic modifications (wild type, *SIRT1* knockout, *LKB1* knockout). 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, PGC1 α 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 2 recent data-driven modeling studies addressing different questions in different models (1, 4). Given that PGC1 α integrates signals from NAD⁺ (via SIRT1) and AMP (via AMPK) (10), 2 key metabolites associated with several biochemical reactions consuming or producing energy, these findings provide further confirmation of 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.

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