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CIRCADIAN RHYTHMS

PARP1 feeds into clocks

> PARP1 participates in linking circadian oscillators to metabolic cues

Feeding patterns can reset molecular clocks in peripheral organs, and links have also been emerging between metabolic signalling and these oscillators. Asher *et al.* now provide new insights into how these two effects are connected with the finding that poly(ADP-ribose) polymerase 1 (PARP1) acts in a pathway that links feeding to control of peripheral clocks.

Cellular levels of the metabolite NAD^+/NADH oscillate daily and regulate other enzymes that are important for clock control. Asher *et al.* therefore asked whether another NAD^+-dependent enzyme, PARP1, might also be important for circadian functions. They found that PARP1 activity in the mouse liver is rhythmic and that the peak of this activity can be altered by changes in feeding patterns.

Next, they looked at how PARP1 might affect the clock circuitry. They found that PARP1 co-immunoprecipitates with two core clock regulators, CLOCK and BMAL1, and that this association peaks at the time when PARP1 activity is maximal. In other contexts, PARP1 can regulate the activity of transcription factors both through protein–protein interactions and through poly(ADP-ribosyl)ation of targets. Here, they found that the interaction of PARP1 with CLOCK is direct and that PARP1 can also directly poly(ADP-ribosyl)ate CLOCK *in vitro* and *in vivo* in a rhythmic pattern. Furthermore, loss of PARP1 disrupts both the association of CLOCK–BMAL1 heterodimers with target genes and the normal timing of CLOCK–BMAL1 interactions with other core clock proteins.

Feeding time has previously been found to be the most dominant parameter for synchronizing circadian gene expression in the liver and other peripheral organs. Importantly, Asher *et al.* observed that PARP1 seems to be important for the effects of altered feeding patterns on clock regulation. Indeed, in mice deficient for PARP1, the phase of circadian gene expression in liver cells responded more slowly to imposed feeding regimens. This suggests that PARP1 participates in linking circadian oscillators to metabolic cues.

A key question now is how PARP1 activity is regulated by feeding cycles. NAD^+ levels are a good candidate and are known to cycle daily in mammals. However, at least *in vitro*, these were not sufficient to account for the daily oscillations in PARP1 activity. The authors also found that the PARP1 BRCT domain, which is known to regulate protein–protein interactions, is crucial for PARP1 activity. So perhaps further analysis of this region will yield insights into how PARP1 is being regulated by feeding.

Alison Schuldt

ORIGINAL RESEARCH PAPER Asher, G. *et al.* Poly(ADP-ribose) polymerase 1 participates in the phase entrainment of circadian clocks to feeding. *Cell* **142**, 943–953 (2010)
FURTHER READING Zhang, E. E. & Kay, S. A. Clocks not winding down: unravelling circadian networks. *Nature Rev. Mol. Cell Biol.* **11**, 764–766 (2010)