A Licensing Mechanism in the Mammalian Circadian Clock Feedback Loop

Alfred G. Tamayo¹, Maria S. Robles², Hao A. Duong¹, Charels J. Weitz¹

¹Harvard Medical School, Boston, MA, UNITED STATES
²Max Planck Institute, Munich, GERMANY

Core clock components regulate transcription by assembling a diverse array of transcriptional co-regulators at the promoters of clock target genes. Here we report that the mouse CLOCK-BMAL1 heterodimer recruits Damaged DNA Binding Protein 1 (DDB1) to gene promoters. Recent studies demonstrate a role for DDB1 in the mono-ubiquitination of histones as part of a complex with the Cullin-4 ubiquitination machinery. We show that depletion of DDB1 in cells results in a significant reduction of H2B mono-ubiquitination at Per1 and Per2 E-box sites. Furthermore, our results demonstrate that DDB1 plays a role in the transcriptional repression of clock target genes by enhancing PER repressor complex occupancy at gene promoters. These observations suggest that CLOCK-BMAL1 directed chromatin modifications license the PER complex for optimal transcriptional repression; a mechanism contributing to the fidelity and precision of the circadian feedback loop.