

## Circadian Clock Genes and the Transcriptional Architecture of the Clock Mechanism

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The molecular mechanism of circadian clocks in mammals is generated by a set of genes forming a transcriptional autoregulatory feedback loop. The “core clock genes” include: *Clock*, *Bmal1*, *Per1*, *Per2*, *Cry1* and *Cry2*. The discovery of “clock genes” led to the realization that circadian gene expression is widespread throughout the body and that the clock is cell autonomous. The cellular autonomy of circadian clocks has raised a number of questions concerning synchronization and coherence of rhythms at the cellular level as well as circadian organization at the systems level. The role of clocks in peripheral tissues has a number of important implications for disease.

In the circadian clock mechanism, CLOCK and BMAL1 activate the transcription of the *Period* and *Cryptochrome* genes. The PERIOD and CRYPTOCHROME proteins then feedback and repress their own transcription by interaction with CLOCK and BMAL1. In the mouse liver, CLOCK and BMAL1 interact with the regulatory regions of thousands of genes, which are both cyclically and constitutively expressed. These target genes are highly enriched for metabolic pathways and indeed all fundamental metabolic pathways in the cell are direct targets of CLOCK:BMAL1. In addition to transcriptional control, the circadian system impacts the timing of metabolism with respect to body weight regulation, aging and longevity. These topics will also be discussed.

1. Takahashi, J.S. 2017. Transcriptional architecture of the mammalian circadian clock. *Nature Rev Genet.* **18**: 164-179.
2. Acosta-Rodriguez, V.A., M.H.M. de Groot,<sup>[1]</sup> F. Rijo-Ferreira, C.B. Green and J.S. Takahashi. 2017. Mice under caloric restriction self-impose a temporal restriction of food intake as revealed by an automated feeder system. *Cell Metabolism* **26**: 267–277.