CDB SEMINAR

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Molecular insights into the mammalian circadian clock: A link to nuclear receptor-mediated transcription and flexibility of its transcriptional networks

Circadian clocks provide cell-autonomous, free-running rhythms with period lengths of about a day. Organisms use these timing systems to internalize exogenous time. In this fashion, organisms can synchronize to the environmental light:dark phase. The advantage of having these clocks is the ability to anticipate, and hence to prepare for, daily recurring events. Although many metabolic, physiological and behavioral processes are affected by circadian clocks, currently no process is known, which is solely dependent on them. The function of these clocks is more to temporally fine-tune processes, probably to enhance the overall fitness of an organism. The aims of current research on these clocks are to understand their organization and to identify the molecular links to the regulated processes.

In mammals, the circadian clock is based on molecular oscillators consisting of inter-connected transcriptional and post-translational feedback loops. Similar mechanisms are operative e.g. in the somite clock. A pair of transcriptional activators, BMAL1 and CLOCK, activates transcription of the PERIOD (PER) repressors, which together with the CRYPTOCHROME (CRY) proteins more and more repress the *Per* genes themselves. Upon subsequent decay of the PER proteins, another cycle of about a day can occur. Rhythmic expression of the *Bmal1* and *Clock* genes is achieved by alternating activation and repression by the nuclear receptors RORa and REV-ERBa, respectively. All these circadian transcriptional events provoke reversible changes in the local chromatin structure, which resemble transitions from eu- to heterochromatin and *vice versa*.

We recently found an unexpected physical interaction between one of the key repressors, PER2, with nuclear receptors. This kind of interaction does not only enhance circadian amplitude of *Bmal1* gene expression, but also constitutes a link between the circadian oscillator and many metabolic pathways under the control of nuclear receptors. These affect for instance the glucose homeostasis in the liver. As hypothesis, PER2 directly transfers oscillator information to many metabolic pathways via physical interaction with nuclear receptors. In this and many more fashions circadian oscillators govern highly organized transcriptional networks. These allow temporally coordinated sequences of transcriptional events to occur every day, even in tissue-specific manner.

Surprisingly, these sophisticated networks are quite flexible. Analyzing the phase difference in the expression of two BMAL1 and CLOCK regulated genes, *Dbp* and *Rev-Erba*, we uncovered two mechanisms that fine-tune their expression. For *Rev-Erba*, accumulation of its own gene product terminated gradually its expression. For *Dbp*, its transcription was delayed by the binding of CRY1 to the *Dbp* promoter region. Flexibility is created by CRY1. In different external photoperiods, the phase difference between both genes may be abolished or even more extended dependent on the persistence of CRY1 in the nucleus. As consequence, DBP became phase-locked to the transition from the light to the dark phase, which is an important prerequisite to maintain anticipation mediated by this transcription factor. Since the phase of the *Cry1* gene is determined by combination of DBP- and REV-ERBa-binding elements, complex regulatory loops responding to the photoperiod could be envisioned.

Taken together, circadian clocks are sophisticated time-keeping devices based on transcriptional networks. They affect many processes, e.g. the cell cycle and the secretion of neurotransmitters in the brain. Consequently, malfunction of the circadian clock may be associated with the occurence of cancer and neuropathological diseases such as depression. However, our understanding of the complex circadian processes may enable us to come up with new therapeutic concepts.

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