# Molecular Regulation of Core Clock Component, CLOCK:BMAL1 Complex in Circadian System

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Recent studies using genetic and molecular approaches to biorhythms have disclosed fundamental features of molecular circadian clock that is self-sustained and cell-autonomous. The clock machinery relies on remarkably well coordinated genetic networks with transcription-translation feedback loop. CLOCK and BMAL1, forming heterodimeric transcription regulator, are core components of the clock machinery that derives circadian gene expression. In response to resetting stimuli, CLOCK acts as a signalling molecule via $Ca^{2+}$ –dependent protein kinase C pathway, while BMAL1 shuttles between cytoplasm and nucleus, thereby facilitating nuclear accumulation of its binding parter. BMAL1 shuttling appears to be an essential step for transactivation as well as for degradation of CLOCK:BMAL1 complex. BMAL1 is also modified by SUMOylation and SUMO-conjugated BMAL1 is exclusively localized in the nuclear body. In response to resetting stimuli, CREB-binding protein (CBP) plays a key role in a rapid activation of the CLOCK:BMAL1 complex that leads to phase resetting. CBP greatly potentiates the CLOCK:BMAL1-mediated Per 1 transcription and knockdown of CBP by application of specific siRNA severely dampeds circadian oscillation. It appears that CBP recruitment by BMAL1 mediates transactivation of CLOCK:BMAL1 complex. Takne together our study demonstrates that CLOCK and BMAL1 play specialized roles in harmonizing the molecular ciradian clock with distinct post-translationl regulations.