東京大学グローバル COE『統合生命学』特別セミナー

東京大学 大学院理学系研究科 生物化専攻セミナー

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演題：Regulation of transcriptional feedback within the *Drosophila* circadian clock

日時：平成 20 年 7 月 15 日（火）16：30～18：00

場所：東京大学理学部 3 号館 3 階 327 号室

Transcriptional activation by CLOCK-CYC (CLK-CYC) heterodimers and feedback repression by PERIOD-TIMELESS (PER-TIM) heterodimers are essential for circadian oscillator function in *Drosophila*. The function of these transcriptional regulators is regulated by post-translational modifications that alter DNA binding, stability and chromatin modifications. We find that binding of CLK-CYC heterodimers containing hypophosphorylated CLK to E-box elements promotes chromatin modifications that enhance transcriptional activation of *per*, *tim* and other circadian oscillator components. PER protein then begins to accumulate, but in a delayed fashion due to DOUBLE-TIME (DBT) dependent phosphorylation and subsequent stabilization by TIM binding. PER-TIM-DBT complexes then enter the nucleus and bind to CLK-CYC, thus promoting the hyperphosphorylation of CLK, loss of CLK-CYC E-box binding, and transcriptional repression. Recent experiments using the PERΔ mutant, which is unable to bind DBT, and hypomorphic dbt^{ar} and dominant negative $dbt^{K/R}$ mutants suggest that DBT acts as a bridge to recruit other kinase(s) into PER-TIM-DBT-CLK-CYC complexes. Once these kinases enter DBT-PER-CLK complexes they phosphorylate PER and CLK, thereby promoting transcriptional repression. Subsequent phosphorylation of PER and CLK by DBT promotes PER and CLK degradation, thereby relieving transcriptional repression.

References:

Yu, W., H. Zheng, J. H. Houl and P. E. Hardin (2006) PER dependent rhythms in CLK phosphorylation and E-box binding regulate circadian transcription. *Genes Dev*. **20**, 723-733.

Kim, E. Y., H. W, Ko, W. Yu, P. E. Hardin and I. Edery (2007) A DOUBLETIME kinase binding domain on the *Drosophila* PERIOD protein is essential for its hyperphosphorylation, transcriptional repression and circadian clock function. *Mol. Cell. Biol.* **27**, 5014-5028.

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