“Molecular network of mammalian circadian clockwork”

In the mammalian circadian clockwork, CLOCK and BMAL1 bind to E-box DNA cis-elements to transactivate a series of genes including Per and Cry, which in turn suppress their own transcription. We showed circadian phosphorylation of CLOCK and BMAL1 proteins, and MS/MS analysis identified the phosphorylation sites that are important for the suppression of the E-box-dependent transactivation. Furthermore, the catalyzing enzymes of their phosphorylation, JNK and CaMKII, play a pivotal role in the molecular oscillation and in the intercellular coupling. Next-generation sequencer and bioinformatics analysis showed rhythmic DNA-binding of clock proteins, and determined their DNA-binding regions and motifs. Such a molecular network causes dynamic circadian outputs for the adaptation to environmental cycles.

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Date: Tuesday, October 7, 2014
Time: 11:00-12:00
Venue: Room #402, 4F, Health and Medical Science Innovation Laboratory, University of Tsukuba