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An approach to reconstruction of cell cycle oscillation of DnaA activity for replication initiation and transcription regulation

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In *Escherichia coli*, an initiation stage of chromosome replication is a main target to trigger cell cycle progression. DnaA initiator protein binds to chromosomal origin, *oriC*, leading to the initiation reaction. The DnaA activity is regulated by binding of ATP and ADP, and the cellular ratio of the ATP-bound form and ADP-form oscillates during cell cycle. The sliding clamp is a component of the replication machinery. Following replication initiation, the DNA-loaded sliding clamps accumulate behind replication forks [1]. The DNA-loaded clamp promotes hydrolysis of ATP bound on the active DnaA, yielding the inactive ADP-DnaA. Thus, the initiation reaction is regulated in a feedback manner. After completion of replication, the clamps are released from DNA and the feedback regulation of DnaA is withdrawn. Before the next round of replication initiation, the ratio of ATP-DnaA is re-accumulated. Chromosomal loci called DARS are involved in this re-accumulation by promoting a nucleotide exchange reaction from ADP-DnaA to ATP-DnaA. DnaA also serves as a regulator for transcription of several genes. In some of these genes, the transcription regulation activity of DnaA is known to be controlled by its ATP/ADP-binding. Thus, the oscillation cycle of DnaA activity seems to act globally for cell cycle progression. We present our approach to reconstruction of the oscillation cycle of DnaA activity by reproducing the dynamic behavior of the clamp.

[1] Su'etsugu, M. and J. Errington, J., The Replicase Sliding Clamp Dynamically Accumulates behind Progressing Replication Forks in *Bacillus subtilis* Cells, *Molecular Cell*, 41, 720-732, 2011