

The cell cycle and the circadian clock : Dynamics of two coupled cellular rhythms

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This presentation will focus on the dynamics of the cell cycle and its entrainment by the circadian clock. I will first discuss a detailed computational model for the network of cyclin-dependent kinases (Cdks) that controls the dynamics of the mammalian cell cycle. The model contains four Cdk modules regulated by phosphorylation-dephosphorylation, association with Cdk inhibitors, and cyclin synthesis or degradation. Growth factors trigger the transition from a quiescent, stable steady state to self-sustained oscillations in the Cdk network. These oscillations correspond to the repetitive, transient activation of cyclin D/Cdk4-6 in G1, cyclin E/Cdk2 at the G1/S transition, cyclin A/Cdk2 in S and at the S/G2 transition, and cyclin B/Cdk1 at the G2/M transition. The model accounts for major properties of the mammalian cell cycle such as continuous cell cycling in the presence of suprathreshold amounts of growth factor, control of cell cycle progression by the balance between antagonistic effects of the tumor suppressor pRB and the transcription factor E2F, existence of a restriction point in G1, and endoreplication. The model for the mammalian cell cycle shows how the regulatory structure of the Cdk network results in its temporal self-organization, leading to the repetitive, sequential activation of the four Cdk modules that brings about the orderly progression through the cell cycle phases. I will next show that the coupling of the cell cycle to the circadian clock can lead to synchronization of these two major cellular rhythms. Entrainment of the cell cycle by the circadian clock may occur through several modes of coupling based on the circadian control of cell cycle proteins such as cyclin E, kinase Wee1, and the Cdk inhibitor p21.

References

- [1] Gérard C, Goldbeter A (2009), *Temporal self-organization of the cyclin/Cdk network driving the mammalian cell cycle*. Proc Natl Acad Sci USA 106, 21643-21648.
- [2] Gérard C, Goldbeter A (2012), *Entrainment of the mammalian cell cycle by the circadian clock: Modeling the dynamics of two coupled cellular rhythms*. PLoS Comput. Biol. 8(5): e1002516. doi:10.1371/journal.pcbi.1002516