DOI 10.18699/SBB-2022-104

A novel and robust molecular switch actuating the quantitative model of eukaryotic Cdk control

Barberis M.

Systems Biology, School of Biosciences and Medicine and Centre for Mathematical and Computational Biology, CMCB, University of Surrey (UOS), Guildford, United Kingdom
Swammerdam Institute for Life Sciences, University of Amsterdam (UvA), Amsterdam, Netherlands
** matteo@barberislab.com; m.barberis@surrey.ac.uk*

Key words: kinetic modeling, network motifs, cell cycle dynamics, transcriptional regulation, budding yeast

Motivation and Aim: The eukaryotic cell cycle is driven by waves of cyclin-dependent kinase (cyclin/Cdk) activities that rise and fall with a timely pattern called "waves of cyclins". This pattern guarantees coordination and alternation of DNA synthesis with cell division, and its failure results in an abnormal cell proliferation. Although details about transcription of cyclins – the regulatory subunits of Cdk – are available [1], a lack of understanding exists about network designs responsible for timely waves of cyclins.
Methods and Algorithms: We have recently identified a transcriptional mechanism that regulates the timing of waves of mitotic cyclin (Clb) in budding yeast. This mechanism involves the evolutionarily conserved Forkhead (Fkh) transcription factors which synchronize Clb appearance. We have also shown that cyclin/Cdk-mediated positive feedback loops (PFLs) and Clb3-centered regulations sustain cyclin/Cdk autonomous oscillations. Here, through a computational and experimental strategy, we reveal a novel and robust molecular design that ensures cell cycle time keeping through interlocking transcription with cyclin/Cdk dynamics in budding yeast. Deterministic and stochastic analyses of thousand structures of a minimal kinetic model of the mitotic cyclin (Clb)/Cdk1 network are verified against *in vivo* quantitative data of Clb dynamics, for their ability to generate Clb waves.
Results: A novel molecular switch is unraveled that identifies a transcriptional cascade through Fkh. The Fkh-mediated cascade among Clb cyclins and Clb/Cdk1-mediated PFLs are pivotal for synchronizing Clb/Cdk1 waves. Furthermore, our model predicts a definite Fkh activation pattern underlying this design, with a progressive Clb/Cdk1-mediated Fkh phosphorylation. Experimental validation confirms the prediction, highlighting the Clb/Cdk–Fkh axis being pivotal for a timely pattern of waves of cyclins.
Conclusion: This work rationalizes the quantitative model of Cdk control for budding yeast, identifying regulatory motifs in place that keep a well-timed cell cycle. Altogether, our effort reveals a conserved, functional design principle in cell cycle control [3].
Acknowledgements: The study is supported by the UvA-Systems Biology Research Priority Area Grant and by the Systems Biology Grant of the University of Surrey.

References

1. Haase S.B., Wittenberg C. Topology and control of the cell-cycle-regulated transcriptional circuitry. *Genetics*. 2014;196(1):65-90.
2. Barberis M. Cyclin/Forkhead-mediated coordination of cyclin waves: an autonomous oscillator rationalizing the quantitative model of Cdk control for budding yeast. *NPJ Syst Biol Appl*. 2021;7(1):48.
3. Barberis M. Quantitative model of eukaryotic Cdk control through the Forkhead CONTROLLER. *NPJ Syst Biol Appl.* 2021;7(1):28.