

Anatomy of a Cell Cycle Checkpoint: The Dynamics of MPF, Cdc25, and Chk1

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ABSTRACT

Cell cycle checkpoints are control mechanisms for ensuring the correct timing of events in the cell cycle and the accurate replication of the genome to daughter cells. We have investigated the dynamics of one particular checkpoint involving the phosphatase Cdc25, the mitosis-inducing kinase Cdc2/CycB (MPF, Maturation Promoting Factor), and the DNA damage activated kinase Chk1. These interactions regulate the response of the cell cycle to DNA damage in the fission yeast *S. pombe*. As a starting point, we model this system as two linked phosphorylation-dephosphorylation (PD) cycles originally formulated by Aguda [1]. Cdc25 dephosphorylates Cdc2 on Thr14 and Tyr15 producing active MPF; MPF in turn activates Cdc25 by phosphorylating its N-terminal regulatory domain.

In this work, we examine these dynamics in more detail. First, we demonstrate that the inhibitory phosphorylation of Cdc25 at Ser216 by Chk1 produces a regulatable switch in which the switching threshold depends on the extent of DNA damage. This checkpoint represents a balance between mitosis-promoting and mitosis-inhibiting signals. Second, we show that the existence of residual activity for the “inactive” forms of Cdc25 and MPF abolishes the transcritical bifurcation described by Aguda [1], but preserves the overall switch-like behavior of the system. Finally, we examine the robustness of this checkpoint control system to internal and external noise.

REFERENCES

- [1] Aguda, B. D. Instabilities in phosphorylation-dephosphorylation cascades and cell cycle checkpoints. *Oncogene*, 18, 2846-2851 (1999).