Spatial Control Principles in Cell Cycle Regulation

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During the cell cycle, the transition from interphase to mitosis is temporally abrupt, all-or-none in character, and irreversible. Mitosis is triggered by the activation of Cdk1-cyclin B1 and its translocation from the cytoplasm to the nucleus. Positive feedback loops regulate the activation of Cdk1-cyclin B1 and help make the process irreversible and all-or-none in character. We examined whether an analogous process, spatial positive feedback, regulates Cdk1-cyclin B1 redistribution. Using chemical biology approaches and single cell live-imaging, we show that nuclear Cdk1-cyclin B1 promotes the translocation of Cdk1-cyclin B1 to the nucleus. Interestingly, interfering with spatial positive feedback gave rise to Cdk1-cyclin B1 nuclear-cytoplasmic oscillatory dynamics and compromised the timing and synchronicity of subsequent mitotic events. We propose that spatial control principles ensure a rapid, complete, robust and irreversible transition from interphase to mitosis and suggest that bistable spatiotemporal switches may be widespread in biological regulation.

Keywords **— Spatial positive feedback, bistability, oscillations, excitability, design principles, cell cycle regulation,**

EXTENDED ABSTRACT

A. Introduction

MITOSIS is unquestionably one of the most spectacular events in cell biology, as it brings unparalleled morphological changes in the cell. The transition from interphase to mitosis is temporally abrupt, all-or-none in character, and irreversible. Mitosis is triggered by the activation of the Cyclin dependent kinase 1 (Cdk1) and its regulatory sub-unit (cyclin-B1) and their translocation from the cytoplasm to the nucleus. The Cdk1-cyclin-B1 complex spatial distribution is dynamically regulated [1]. During interphase it shuttles between cytoplasm and nucleus with a rapid nuclear export rate, whereas at the onset of mitosis, the active complex translocates to the nucleus in a temporally abrupt, switch-like manner. The activation of the Cdk1:Cyclin-B1 complex results from two interlinked positive feedback loops: Cdk1:Cyclin-B1 activates its own activator, the phosphatase Cdc25, and is in turn inhibited by its own inhibitor, the Wee1 kinase [2]. This topology results in a bistable activation of Cdk1-cyclin B1 complex that help make the mitotic onset irreversible and all-or-none in character. We examined whether an analogous process, *spatial positive feedback*, regulates Cdk1-cyclin B1 cytoplasmic to nuclear redistribution. We approached this question by combining mathematical modeling with quantitative single cell imaging studies.

B. Results

Using chemical biology approaches and single-cell live imaging, we show that nuclear Cdk1-cyclin B1 promotes the translocation of Cdk1-cyclin B1 to the nucleus. Mechanistic studies suggest that cyclin B1 phosphorylation promotes nuclear translocation and, conversely, nuclear translocation promotes cyclin B1 phosphorylation, accounting for the feedback. Modeling studies suggested that Cdk1-cyclin B1 nuclear localization is bistable.

Interestingly, interfering with spatial positive feedback gave rise to Cdk1-cyclin B1 nuclear-cytoplasmic *oscillatory dynamics* with characteristics of an excitable system. Moreover, interfering with the abruptness of Cdk1-cyclin B1 translocation affects the timing and synchronicity of subsequent mitotic events, underscoring the functional importance of spatial positive feedback for fidelity of mitosis [3].

The timing of nuclear envelop break down (NEB) was intrinsically linked to the absolute concentration of Cdk1:Cyclin-B1 in the nucleus, and was notably delayed when the switch like nature of Ckd1:Cyclin-B1 import was perturbed, showing that spatial-temporal regulation of the complex is invaluable for timing of mitotic events.

C. Conclusions

We propose that spatial positive feedback ensures a rapid, complete, robust and irreversible transition from interphase to mitosis and suggest that bistable spatiotemporal switches may be widespread in biological regulation.

REFERENCES

[1] Takizawa CG, Morgan DO (2000) Control of mitosis by changes in the subcellular location of cyclin-B1-Cdk1 and Cdc25C. In *Curr Opin Cell Biol*, 12, pp. 658–65.

[2] Ferrell, JE, *et al* (2009) *FEBS Letters*. 583, pp 3999-4005

[3] Santos, S. Wollman, R, Meyer, T and Ferrell, JE (2012) Spatial Positive Feedback at the Onset of Mitosis. *Cell. In press*

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