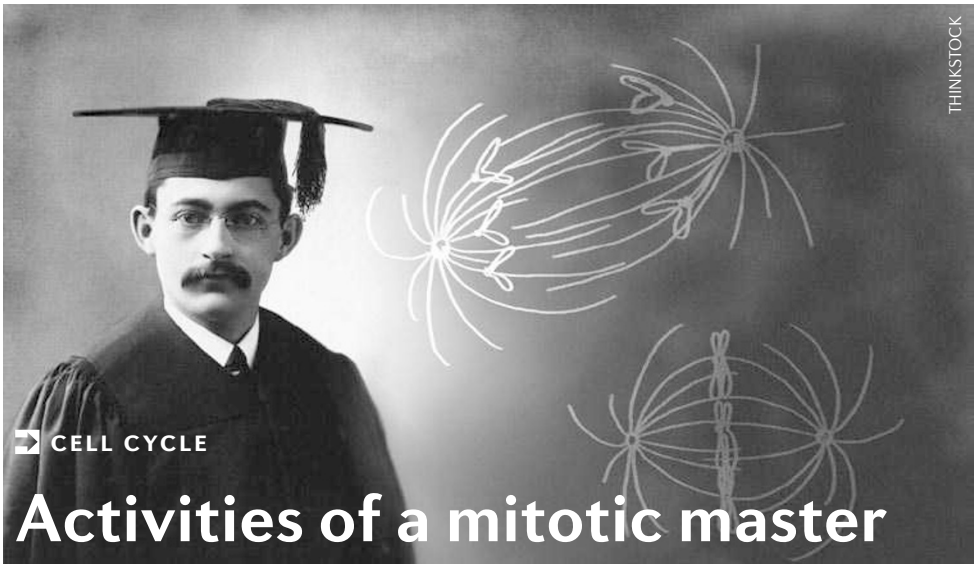

CELL CYCLE

Activities of a mitotic master

In most animal cells, mitosis is triggered by the activation of the cyclin B1-associated cyclin-dependent kinase 1 (CDK1), which phosphorylates a range of substrates, thus promoting cell architecture changes that drive mitosis and cytokinesis. Despite its crucial role in the promotion of mitosis, when and how rapidly cyclin B1–CDK1 is activated in mammalian cells is unclear, as is the mechanism by which its activation coordinates mitotic events in both the cytoplasm and nucleus.

To address these questions, Gavet and Pines developed a Förster resonance energy transfer (FRET)-based biosensor specific for cyclin B1–CDK1 that allows monitoring of its activity with high temporal and spatial precision in living mammalian cells. The FRET biosensor is made of donor and acceptor fluorophores linked by a phosphorylation site that is specifically phosphorylated by cyclin B1–CDK1, and a phosphobinding domain that binds to CDK phosphorylation sites *in vivo*. On phosphorylation, binding of the phosphobinding domain induces a conformational change that alters FRET efficiency between donor and acceptor, which can be quantified.

As reported in *Developmental Cell*, the authors used this biosensor to show that cyclin B1–CDK1 is inactive in G2 phase and begins to be activated only at the start of prophase, at a set time before nuclear envelope breakdown (NEBD). Low levels of cyclin B1–CDK1 activity induce cell rounding, thereby initiating the events of prophase, as well as cyclin B1–CDK1 import in the nucleus and subsequent activation of the anaphase-promoting complex (APC; also called the cyclosome), which is required for cyclin B1 degradation. The activity of cyclin B1–CDK1 increases gradually, reaching a maximum in ~30 minutes, and high activity in prophase was found to be required for disassembly of the nucleolus and NEBD. The high activity remains constant throughout prometaphase and metaphase and drops sharply at the beginning of anaphase, when cells exit mitosis.

In a separate study published in the *Journal of Cell Biology*, Gavet and Pines investigated what triggers the nuclear accumulation of cyclin B1–CDK1. Cyclin B1 shuttles between the nucleus and cytoplasm in interphase and is mostly cytoplasmic before rapidly accumulating in the nucleus at prophase. This was previously thought to be a result of inhibition of cyclin B1 nuclear export by Polo-like kinase 1 (PLK1). At prophase, activating cyclin B1–CDK1 in the cytoplasm immediately triggers rapid accumulation of the complex in the nucleus owing to a 40-fold increase in nuclear import. Although cyclin B1–CDK1 nuclear import during interphase was affected by CDK- and PLK1-dependent phosphorylation, it was unaffected by PLK1 and the export machinery during prophase. Finally, the authors show that cyclin B1–CDK1 nuclear accumulation remains dependent on CDK1 activity until NEBD and that a substantial proportion of active cyclin B1–CDK1 remains in the cytoplasm during prophase.

Together, these studies show that different levels of cyclin B1–CDK1 activity trigger different mitotic events and that activation of cyclin B1–CDK1 promotes its rapid nuclear import, thus revealing how the remarkable reorganization of the nucleus and the cytoplasm are coordinated at mitotic entry.

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FURTHER READING Hochegger, H., Takeda, S. & Hunt, T. Cyclin-dependent kinases and cell-cycle transitions: does one fit all? *Nature Rev. Mol. Cell Biol.* **9**, 910–916 (2008)