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Spotlight

The yin and yang of nuclear envelope breakdown through the activity of phosphatase holoenzyme PP2A-B55^{SUR-6}

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Cell division is a highly regulated and guardedly orchestrated process including nuclear envelope breakdown (NEBD). A recent study from Kapoor, Adhikary, and Kotak identifies the symphonic role of a phosphatase holoenzyme in NEBD.

The yin and yang of protein phosphorylation and signaling (Figure 1, top panel) [1] symbolizes a balance between two opposite forces. The reversibility of protein phosphorylation may not always be a simple on-or-off switch leading to signaling and amplification, but rather may be a harmonic opposition of forces toward an outcome (Figure 1) [1]. In higher eukaryotes, the phosphorylation balance coordinates NEBD and ensures the accurate segregation of the genetic material. NEBD is a fork in the road of mitosis. The correct, well-timed path allows microtubule/mitotic spindle connections to the chromatids for the segregation toward metaphase plate alignment and continued cell division. The misguided path leads to incomplete nuclear envelope (NE) disassembly, improper segregation, and multinucleation.

Several lines of evidence point to kinase-directed phosphorylation at the onset of mitosis as the primary regulatory mechanism of NEBD [2–5]. Substates of these kinases are mainly found in the NE, nuclear pore complex (NPC), and nuclear lamina (Figure 1, bottom panel) [5]. The possible role of phosphatase and the total balance between kinases and phosphatases in mitotic NEBD is largely neglected. Yet, it is recognized that the erroneous activity of phosphatases can lead to tumorigenesis [6]. The holoenzyme PP2A-B55 is one of the major serine/threonine phosphatases involved in controlling many signaling cascades [6]. The trimeric holoenzyme consists of a catalytic (C), scaffold (A), and regulatory (B) subunit. Cryogenic electron microscopy (cryo-EM) structures of PP2A-B55 holoenzyme confirm multiple binding sites on the regulatory B55 subunit for substrate and inhibitor exchange, starts to provide a molecular roadmap to the design of PP2A-B55 [7]. Several lines of evidence point to its potential role as a tumor suppressor [6]. Hence, misregulation from its B subunit may lift its constancy. Overexpression of cancerous inhibitors of PP2A-B55 is found in a variety of human cancers, including breast, ovarian, colon, and non-small cell lung carcinoma [6].

A recent paper by Kapoor, Adhikary, and Kotak in *Cell Reports* characterizes an unanticipated role of the PP2A phosphatase B55^{SUR-6} (PP2A-B55^{SUR-6}) holoenzyme activity in NEBD (Figure 1, bottom panel) [8]. B55^{SUR-6} serves as a regulatory B subunit within this holoenzyme [8]. The authors used the cell division of the one-cell *Caenorhabditis elegans* embryo to investigate NEBD during the first embryonic division. Mitotic spindles form outside the NE, and the whole NE, must disintegrate to facilitate chromosome separation. This study identified PP2A-B55^{SUR-6} as essential for timely nuclear envelope permeabilization (NEP) and complete NE disassembly. This discovery helps greatly to simplify the yin and yang vision of signals harmonizing NEBD (Figure 1, bottom panel). It also reveals that PP2A-B55^{SUR-6} targets multiple paths to synchronize the onset of accurate NEBD.

Drivers of NEBD are the yin and yang balance of kinase/phosphatase at the NE/NPC/lamina and microtubule and dynein-dependent forces inside and outside the nucleus and at the NE [5,8,9]. The formation of the mitotic spindles rests outside of intact pre-mitotic NE. At the NE, signals need to begin to cue the dismantling of the NPC and depolymerization of the lamina. NEBD leads to the collapse of the Ran-GTP gradient, puts a hold on nuclear transport, and produces a mixture of nuclear and cytoplasmic macromolecules for NEP [5]. Mitotic spindles are free to direct microtubular attachment to the centromere-formed kinetochores of the chromatids and eventual metaphase plate formation.

In Kapoor, Adhikary, and Kotak's *Cell Reports* article, the major evidence is the knockdown of B55^{SUR-6}, leading to multi-nuclei formation and lack of microtubule movement [8], as previously seen in temperature-sensitive mutants [10]. Throughout PP2A-B55^{SUR-6} deletion, NPC stays intact, lamin fails to be torn or broken away from the NE, and improper segregation occurs. These results illustrate the importance of a functional complete phosphatase in NEBD. The holoenzyme PP2A-B55^{SUR-6} is essential for the well-timed tearing down of NE by bringing together microtubular/dynein forces, dismantling the NPC, and ripping the lamin (LMN-1) away from the NE (Figure 1).

These findings add to the significance of PP2A-B55 activity in mitosis, and its critical regulatory function, and warrant characterizing disease-associated mutations and potential avenues to target this holoenzyme therapeutically [7,8]. In this case, PP2A-B55^{SUR-6}, specifically the B55^{SUR-6} subunit, begins to meet the criteria of tumor suppressor gene by embodying the opposing force to maintain the yin and yang governing NEBD and, therefore, the harmony of cell proliferation [8]. Further structural studies combined with

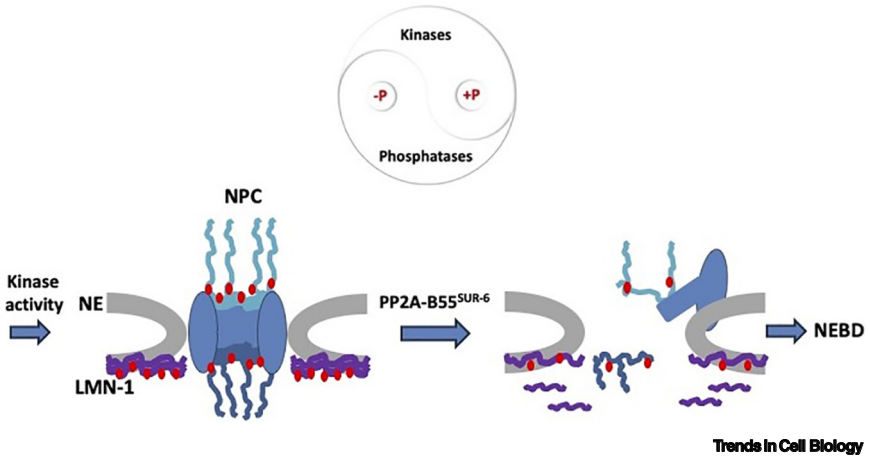

Figure 1. The yin and yang of protein phosphorylation and signaling. Top panel, taijitu, symbolizes a balance between two opposite forces. PP2A-B55^{SUR-6}-reliant nuclear envelope (NE) disassembly at the first-embryonic division of *Caenorhabditis elegans*. Within the embryos, the import of PP2A-B55^{SUR-6} into the nucleus harmonizes the progress of dismantling the NE by removing phosphates from the lamina LMN-1 (purple) and nuclear pore complex (NPC) (blue-green), while altering microtubular/dynein organization (not shown), leading to eventual nuclear envelope breakdown (NEBD) (bottom panel).

phosphoproteomics analysis of PP2A-B55^{SUR-6} will allow for the identification of dephosphorylation sites on LMN-1, several Nups, and possible microtubule/dynein substrates [8]. In summary, the yin and yang balance of NEBD is a significant step in mitosis and the harmonic control by PP2A-B55^{SUR-6} makes it a target for therapeutic development.

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Declaration of interests

No interests are declared.

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References

1. Hunter, T. (1995) Protein kinases and phosphatases: the yin and yang of protein phosphorylation and signaling. *Cell* 80, 225–236
2. Laurell, E. *et al.* (2011) Phosphorylation of Nup98 by multiple kinases is crucial for NPC disassembly during mitotic entry. *Cell* 144, 539–550
3. Nkombo Nkoula, S. *et al.* (2023) Mechanisms of nuclear pore complex disassembly by the mitotic Polo-like kinase 1 (PLK-1) in *C. elegans* embryos. *Sci. Adv.* 9, eadf7826
4. Maryu, G. and Yang, Q. (2022) Nuclear-cytoplasmic compartmentalization of cyclin B1-Cdk1 promotes robust timing of mitotic events. *Cell Rep.* 41, 111870
5. Kutay, U. *et al.* (2021) Mitotic disassembly and reassembly of nuclear pore complexes. *Trends Cell Biol.* 31, 1019–1033
6. Goguet-Rubio, P. *et al.* (2020) PP2A-B55 holoenzyme regulation and cancer. *Biomolecules* 10, 1586
7. Padi, S.K.R. *et al.* (2024) Cryo-EM structures of PP2A:B55-FAM122A and PP2A:B55-ARPP19. *Nature* 625, 195–203
8. Kapoor, S. *et al.* (2023) PP2A-B55(SUR-6) promotes nuclear envelope breakdown in *C. elegans* embryos. *Cell Rep.* 42, 113495
9. Heald, R. and McKeon, F. (1990) Mutations of phosphorylation sites in lamin A that prevent nuclear lamina disassembly in mitosis. *Cell* 61, 579–589
10. O'Rourke, S.M. *et al.* (2011) A survey of new temperature-sensitive, embryonic-lethal mutations in *C. elegans*: 24 alleles of thirteen genes. *PLoS One* 6, e16644