JCB Journal of Cell Biology

SPOTLIGHT

Oiling the wheels of nuclear division: SUMOylation regulates the expansion of the mitotic nuclear membrane

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Eukaryotic cell division involves the segregation of chromosomes between two daughter cells and must be coordinated with extensive rearrangement of their nuclear envelopes. In this issue, Saik et al. (2023 *J. Cell Biol.* https://doi.org/10.1083/jcb.202208137) show that a SUMOylation cascade at the inner nuclear membrane elevates the levels of phosphatidic acid, a key phospholipid precursor, to support the need for nuclear membrane expansion during mitosis.

The cytology of nuclear division has long fascinated cell biologists. Eukaryotes employ two contrasting strategies to divide their nuclei (1): (a) "open mitosis," which predominates in metazoans and where the nuclear envelope breaks down at the onset of mitosis before re-assembling in a stepwise manner around the segregated chromosomes; and (b) "closed mitosis," where mitotic spindle assembly and chromosome segregation take place within the confines of an intact and elongating nuclear envelope and which is common in the fungal kingdom. Both strategies depend on mechanisms that provide new membranes to support daughter nuclei formation in a timely manner. Exactly how that happens remains a fundamental question in the field. Previous studies have shown that excess phospholipid synthesis can lead to nuclear membrane expansion, suggesting that the spatiotemporal activation of the phospholipid enzymatic machinery participates in nuclear growth (2, 3). The study by Saik et al. (4) now provides important new insights into the regulation of this process during "closed" mitosis in budding yeast.

In previous work, the authors reported that during mitosis the nuclear E3 SUMO ligase Siz2 associates with the VAP protein Scs2 at the inner nuclear membrane (INM) in a phosphorylation-dependent manner (5). Phospho-Siz2 then initiates a wave of SUMOylation, which is responsible for the re-association of chromatin with the nuclear envelope at later mitotic stages (5). Because Siz2 binding to the INM coincides with the onset of nuclear elongation, the authors asked whether Siz2-mediated SUMOylation also directs mitotic nuclear membrane expansion. To address this, Saik et al. (4) first examined the impact of modifying the INM association of Siz2 on nuclear expansion. They found that a Siz2-phosphorylation deficient mutant that is unable to bind the INM displays reduced nuclear expansion in mitosis, while constitutive INM tethering of Siz2 has the opposite effect, resulting in elevated SUMOylation and nuclear expansion at all cell cycle stages. Consistently, the authors observed increased nuclear membrane expansion in cells lacking the isopeptidase that removes the SUMO modification, but only when Siz2 was present at the INM.

What could be driving this SUMOylation-mediated nuclear membrane expansion? Phosphatidic acid (PA) is a central precursor for the synthesis of the major phospholipids, and previous studies in budding yeast have linked elevated PA levels to nuclear envelope expansion (6). By following the distribution of an intranuclear PA reporter, the authors found that mitotic cells display higher INM PA levels, which require the presence of Siz2 at the INM. Furthermore, constitutive anchoring of Siz2 at the INM resulted in increased PA levels during interphase, when INM PA levels are normally low, consistent with the idea that Siz2 activity elevates PA levels.

Next, the authors investigated the link between Siz2 and the metabolic pathways that regulate PA levels. Pah1 is a member of the evolutionarily conserved lipin family that converts PA to diacylglycerol (7). Inactivation of Pah1 results in elevated PA and phospholipid levels (7) and derepressed endoplasmic reticulum and nuclear membrane expansion (2). Pah1 is inhibited by phosphorylation mediated by several kinases, including Cdk1 during mitosis (8), and activated by dephosphorylation catalyzed by the Nem1-Spo7 membrane-bound complex (2). Remarkably, Saik et al. (4) found that phosphorylated Pah1 could rescue the nuclear expansion defect caused by loss of Siz2-mediated SUMOylation at the INM, while dephosphorylated Pah1 had the opposite effect and reduced excess nuclear expansion driven by high levels of SUMOylation. These genetic interactions supported the model that SUMOylation regulates PA levels by controlling the

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activity of Pah1. The authors then asked whether this regulation takes place by modulating the binding of Pah1 to its activator complex Nem1-Spo7. By performing affinity purifications from synchronized cell cultures, the authors found that the interactions between Pah1 and Spo7, as well as between Nem1 and Spo7, were reduced during mitosis compared to those of interphase. Importantly, in both cases, this reduction was not seen in a Siz2 mutant that is unable to SUMOylate INM targets. Collectively, these data led the authors to propose that Siz2-directed SUMOylation at the INM decreases the formation of Pah1/Nem1-Spo7 complex during mitosis, resulting in the inhibition of Pah1 activity and the build-up of PA to promote phospholipid and nuclear membrane expansion. The fact that Pah1 and Nem1-Spo7 are found in the cytoplasm and nucleus while Siz2 is restricted inside the nucleus suggests that SUMOylation acts as a compartmentalized switch to inactivate the nuclear pool of Pah1.

The molecular basis of how SUMOylation reduces the formation of the Pah1/Nem1-Spo7 complex remains unknown: the authors did not detect any SUMOylation on Pah1, Nem1, or Spo7, so further work will be needed to determine whether other Siz2 targets at the INM interfere with complex formation. Moreover, no apparent changes in the mitotic phosphorylation of Pah1 were seen in Siz2 mutants, although this could be due to technical reasons. Given the critical role of mitotic lipin phosphorylation for "closed" mitosis (9), additional work will be required to clarify mechanistically how SUMOylation impacts Pah1 phosphorylation and activity. Interestingly, while Siz2-directed SUMOylation is clearly required for efficient mitotic nuclear membrane expansion, loss of Siz2 activity at the INM did not prevent nuclear membrane growth at other stages of the cell cycle; moreover, dividing nuclei of siz2 mutants appear to be able still to accommodate "closed" mitosis. These observations suggest the presence of additional pathways controlling nuclear growth. These may involve nuclear Pah1, or different lipid metabolic pathways in the nucleus that provide the necessary membrane. Alternatively, the endoplasmic reticulum, which is continuous with the nuclear membrane, could feed additional membrane components. The work by Saik et al. (4) now provides the tools to probe these mechanisms genetically and determine their relative contributions to nuclear membrane growth during the cell cycle.

Overall, Saik et al. (4) provide significant novel evidence of a cell cycle–regulated pathway that rewires lipid metabolism at the INM to facilitate mitotic nuclear membrane expansion. These findings emphasize the emerging view of nuclear lipid metabolism as an active component of cell physiology (10). Further work will be required to dissect the mechanistic details underlying the role of SUMOylation in nuclear membrane growth.

Acknowledgments

The work in the author's laboratory is funded by the Biotechnology and Biological Sciences Research Council (BB/T005610/1).

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