A SUMOylation wave to anchor the genome

Adele L. Marston

Chromatin tethers to the nuclear envelope are lost during mitosis to facilitate chromosome segregation. How these connections are reestablished to ensure functional genome organization in interphase is unclear. Ptak et al. (2021. J. Cell Biol. https://doi.org/10.1083/jcb.202103036) identify a phosphorylation and SUMOylation-dependent cascade that links chromatin to the nuclear membrane during late mitosis.

Eukaryotic genomes are surrounded by a nuclear membrane that influences chromatin folding by providing an interaction surface (1). Transcriptionally silent heterochromatin preferentially associates with the inner nuclear membrane, while nuclear pore complexes tend to interact with transcriptionally active chromatin. Chromatin tethering to the nuclear envelope (NE) is linked to telomere length regulation, gene silencing, and DNA damage repair (2). However, in mitosis, chromatin-nuclear envelope contacts need to be broken to prevent chromosome segregation errors (3). How chromatin contacts are reestablished after mitosis remains elusive. In this issue, Ptak et al. (4) took advantage of budding yeast, where unlike in mammals, the nuclear membrane remains largely intact during mitosis (5), to address this question.

Small ubiquitin-related modifier (SUMO) is an ~10-kD polypeptide that is post-translationally and reversibly attached to proteins (6). SUMO has been implicated in tethering chromatin to the NE (7). Using immunofluorescence and an antibody against yeast SUMO protein (Smt3), the authors found that SUMO conjugates are concentrated at the NE in mitosis but not interphase. Mitosis-specific SUMO conjugates were predominant in the 40-55 kD range on immunoblots, leading the authors to screen a panel of 141 mutants deleted for genes encoding known SUMOylated proteins of this molecular weight. Remarkably, the major mitotic SUMO band was missing in cells lacking Scs2 (scs2Δ) or expressing a version of Scs2 that cannot be SUMOylated (scs2K180R). Scs2 is the yeast homologue of the highly conserved VAP (vesicle-associated membrane protein [VAMP]-associated protein) family of integral membrane proteins, which act as receptors for cytoplasmic proteins on the endoplasmic reticulum (8). Ptak et al. found that Scs2 also localizes to the inner nuclear membrane, where it functions as a protein receptor in the nucleus. At least three other proteins also were SUMOylated in mitosis, which was largely abolished in cells lacking Scs2 (scs2Δ) or expressing a version of Scs2 that cannot be SUMOylated (scs2K180R). Together, these observations suggested that SUMO conjugation to Scs2 triggers a wave of mitosis-specific SUMOylation of yet-unidentified targets.

Using yeast genetics, the authors identified that Siz2 was the SUMO E3 ligase responsible for the enrichment of Scs2-SUMO and mitotic SUMOylated species at the NE. Imaging of cells revealed that Siz2 itself relocates abruptly from the nucleoplasm to the NE in late mitosis as a consequence of its phosphorylation on serine 522. Thus, preventing Siz2 phosphorylation abolishes the wave of SUMOylation at the NE that is normally observed in mitosis. Therefore, Siz2 phosphorylation allows it to bind Scs2 via the FFAT-MSP interaction, resulting in Scs2 SUMOylation. Scs2-SUMO in turn, reinforces the FFAT-MSP interaction, or by abolishing the SUMO acceptor site on Scs2. Interestingly, chromatin tethering persisted into G1 while Scs2 SUMOylation and Siz2 phosphorylation did not. This suggested that while phosphorylation and SUMOylation control the establishment of chromatin tethering,
maintenance of the NE interactions is under distinct regulation. Telomere association with the NE in mitosis is known to require Sir4, which is itself SUMOylated (\(^7\)). The authors found that although Siz2 association with the NE in mitosis is known to be regulated, the specific roles of Siz2 and Sir4 are not well understood. Telomere association with the NE is also regulated by SUMOylation, though the exact mechanisms and targets are not yet fully clear.

Overall, Ptak et al. showed that mitotic phosphorylation triggers a wave of SUMOylation at the NE to re-attach chromatin to the nuclear periphery in late mitosis (Fig. 1). Their work revealed a multilayered mechanism of complex formation between Siz2 and NE-Sir4. SUMOylation of an unknown target also leads to the recruitment of the INO1 gene to nuclear pores. Telomeres were not the only chromatin loci whose tethering depended on Scs2- and Siz2-mediated NE SUMOylation. The INO1 gene relocates to the nuclear pore complex when activated in response to inositol starvation and this regulation had previously been linked to Siz2 SUMOylation (\(^9\), \(^10\)). INO1 relocalization occurred in G1 and late mitosis, but not in S phase, and required both Siz2 phosphorylation and Scs2 SUMOylation. Unlike telomeres, however, INO1 relocalization did not require Sir4 SUMOylation. Hence, NE-directed SUMOylation uses distinct mechanisms to promote the association of telomeres with the NE and INO1 with the nuclear pores. Which is the relevant SUMO target that directs INO1 relocalization from the nucleoplasm to the nuclear pore complex is an intriguing question to be addressed in the future. Some of the other SUMO conjugates that the authors observed in mitosis might hold the solution to this part of the puzzle.

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