JCB Journal of Cell Biology

SPOTLIGHT

Sensing danger at the bridge

Juan Martin-Serrano[1]

NoCut safeguards genome integrity against persistent DNA bridges, but how these missegregation events are sensed is not understood. In this issue, Dam et al. (https://doi.org/10.1083/jcb.202502014) identify the Srs2 and PARI helicases as conserved NoCut sensors that initiate signalling to delay cytokinetic abscission.

Chromosome missegregation events pose major threats to genome stability (1). Chromosomes that are not captured by the mitotic spindle are sensed by the spindle assembly checkpoint (SAC) that monitors the kinetochore-microtubule attachments during metaphase (2). The SAC delays anaphase upon sensing lagging chromosomes, buying time until all chromosomes are attached and aligned. Unlike lagging chromosomes, persistent DNA bridges go under the SAC radar as these bridges retain kinetochore-microtubule attachments. These DNA bridges can have different origins, such as dicentric chromosomes that are chromatinized. Alternatively, persistent interchromatid entanglements that are not chromatinized, known as ultrafine DNA bridges (UFBs), can originate from defects in DNA replication and repair (3).

DNA bridges that persist beyond mitotic reformation of the nuclear envelope and cytokinesis can be catastrophic for genetic stability. One common outcome for these events is cytokinesis failure that results in binucleation and tetraploidization (4), features frequently associated with tumor formation. If binucleation is avoided, the next danger is the interphase breakage of the persistent DNA bridge. This rupture initiates iterative cycles of catastrophic chromosomal instability in the next rounds of cell division, including chromosome fusions, chromothripsis, aneuploidy, and micronuclei (5). Persistent chromosome bridges also result in nuclear envelope instability, which threatens the genome as cytoplasmic nucleases can access the compromised nuclear compartment and damage chromatin (6).

Critically, persistent DNA bridges of multiple origins can engage the abscission checkpoint, also known as NoCut, to avoid catastrophic effects on genetic stability (7, 8). In ways that remain poorly understood, the Aurora B kinase is engaged by the presence of DNA bridges beyond anaphase to delay cytokinetic abscission, and this delay correlates with protection against binucleation and genetic damage associated with the rupture of the bridge. In yeast, NoCut acts through BOI2, an exocytosis-associated factor involved in abscission. The mechanism of abscission delay is better understood in mammalian cells as NoCut intersects with the ESCRT machinery, a conserved membrane remodeling pathway that facilitates cytokinetic abscission (9). A key target for NoCut regulation in this context is ESCRT-III, a filament-forming complex that severs the midbody during abscission. The assembly of these filaments requires the dynamic exchange of ESCRT-III subunits, which is driven by the AAA+ ATPase VPS4 to facilitate membrane scission. Once NoCut is engaged, Aurora B phosphorylates CHMP4C, an ESCRT-III regulatory subunit, to delay abscission (10). Sustaining these delays requires the downstream phosphorylation of additional ESCRT-III subunits by ULK3, as well as retention of VPS4 by ANCHR. NoCut also promotes the accumulation of actin patches at DNA bridges to avoid their rupture (4). Thus, the emerging model is that NoCut coordinates multiple cellular pathways to avoid binucleation and breakage of persistent DNA bridges.

A key gap in our understanding of NoCut activity has been the mechanisms to sense the missegregated DNA. Dam et al. shed new light into this question by identifying the helicase Srs2 as a key NoCut factor in yeast (11). The authors use an elegant combination of genetics and live-cell microscopy to show that Srs2 is required to delay cytokinetic abscission in response to chromatin bridges that persist into cytokinesis. More importantly, premature cytokinesis in Srs2-deficient cells results in genetic damage that is associated with persistent chromatin bridges. This protective role is not restricted to chromatin bridges induced by replication stress, as Srs2 is also required to delay abscission in response to catenated chromatin bridges that are induced by inhibition of TOP2. Further mechanistic studies show that Srs2 binding to PCNA is required for NoCut activity, supporting a model whereby signalling from the DNA bridges to NoCut requires the association of Srs2 with the missegregated chromatin. This model is further supported as retention of PCNA and Srs2 on dicentric chromatin bridges, otherwise undetectable by NoCut, is sufficient to trigger abscission delays. This role of Srs2 in abscission regulation seems to be conserved in evolution as PARI, the human homolog of Srs2, is required for NoCut responses to chromatin bridges. NoCut also responds to nuclear pore assembly defects, but this surveillance pathway is not perturbed in PARI-depleted cells, thus highlighting its specific role in chromatin sensing. Lastly, the authors

[1]Department of Infectious Diseases, Faculty of Life Sciences & Medicine, King's College London, London, UK.

Correspondence to Juan Martin-Serrano: juan.martin_serrano@kcl.ac.uk.

show that PARI contributes to the accumulation of actin patches at persistent DNA bridges, providing one plausible mechanism for protection against bridge ruptures.

A recent study has shown that Bloom syndrome helicase (BLM), which contributes to the resolution of UFBs, is required for NoCut sensing of unresolved UFBs that persist beyond anaphase (12). This work also provides evidence that BLM signals to Aurora B by converting dsDNA into RPA-coated ssDNA, further engaging ATR-CHK1. Similarly to the phenotype observed with Srs2, persistent UFBs in BLM-depleted cells results in binucleation and aneuploidy. Besides Srs2/PARI and BLM, topoisomerase II has been proposed as a NoCut sensor of chromatin bridges (13). One important caveat with this model is that persistent bridges induced by low doses of topoisomerase II inhibitors can be sensed by NoCut, although partial topoisomerase II activity may be sufficient for chromatin sensing in this context. Collectively, these findings raise the intriguing possibility that UFBs and bulky chromatin bridges may be sensed by different factors that could be determined by the composition and origin of the missegregated DNA, although this model requires further work. Critically, it remains unclear how these sensors connect with the effectors of cytokinetic abscission such as the Boi2 in yeast, the ESCRT machinery in mammalian cells, and the actin cytoskeleton.

Despite progress in this field, the mechanisms of genome protection by NoCut remain poorly understood beyond avoiding binucleation. In the case of persistent UFBs, delaying abscission could give extra time to BLM and other UFB-resolving factors to disentangle the missegregated DNA, but it is less clear how a chromatin bridge could be resolved in this context. One emerging concept is that coordinated regulation of membrane remodeling and actin patches may prevent the rupture of the bridge, thus avoiding DNA breakage and the subsequent catastrophic consequences for genome stability. This model is consistent with the premature rupture of DNA bridges when CHMP4C is depleted (10). Crucially, it is becoming increasingly clear that genome protection by NoCut plays important roles in cancer. A CHMP4C allele that predisposes carriers to ovarian and other cancers fails to sustain NoCut, leading to elevated DNA damage under conditions that increase the frequency of persistent DNA bridges (14). Similarly, the connection between BLM and NoCut provides plausible mechanisms to explain cancer predisposition in individuals with Bloom's syndrome (12). In this context, future studies to reveal how sensing DNA bridges by PARI protects the genome will inform new oncogenic mechanisms (Fig. 1).

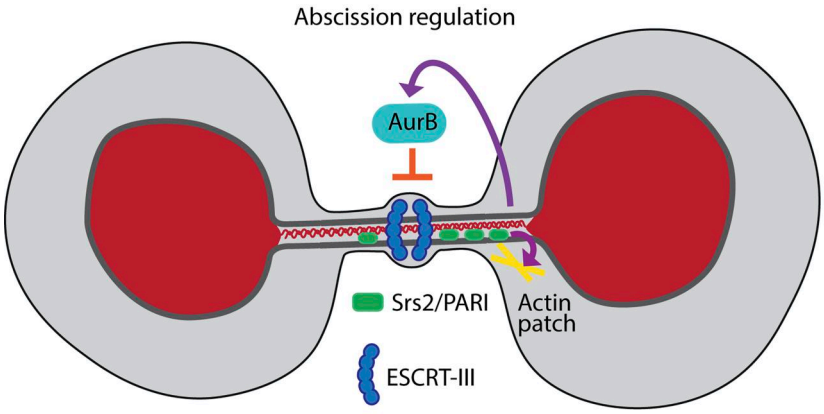

Figure 1. **Abscission regulation by NoCut requires the Srs2/PARI helicases.** DNA missegregation events that persist beyond cytokinesis engage the NoCut pathway to protect the genome. Dam et al. show that the Sr2s helicase participates in the sensing of missegregated DNA in yeast, and a similar role is proposed for PARI, the human homolog of Srs2. Sensing of the missegregated DNA by these helicases is proposed to initiate a signalling cascade through Aurora B, thereby inhibiting mediators of abscission such as the ESCRT machinery. Parallel induction of actin patches contributes to stabilize the DNA bridges, thus avoiding catastrophic DNA damage.

Acknowledgments

Research in Juan Martin-Serrano laboratory is funded by Biotechnology and Biological Sciences Research Council (BB/Y004205/1). Reference limits prevented me from citing all relevant studies; I apologize for any omissions.

Author contributions: Juan Martin-Serrano: conceptualization, funding acquisition, and writing—original draft, review, and editing.

Disclosures: The author has completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest, and none were reported.

References

1. Santaguida, S., and A. Amon. 2015. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/nrm4025
2. McAinsh, A.D., and G.J.P.L. Kops. 2023. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/s41580-023-00593-z
3. Fernandez-Casanas, M., and K.L. Chan. 2018. *Genes (Basel)*. https://doi.org/10.3390/genes9120623
4. Steigemann, P., et al. 2009. *Cell*. https://doi.org/10.1016/j.cell.2008.12.020
5. Umbreit, N.T., et al. 2020. *Science*. https://doi.org/10.1126/science.aba0712
6. Maciejowski, J., et al. 2015. *Cell*. https://doi.org/10.1016/j.cell.2015.11.054
7. Agromayor, M., and J. Martin-Serrano. 2013. *Trends Cell Biol.* https://doi.org/10.1016/j.tcb.2013.04.006
8. Mendoza, M., and Y. Barral. 2008. *Biochem. Soc. Trans.* https://doi.org/10.1042/BST0360387
9. Vietri, M., et al. 2013. *Nat. Rev. Mol. Cell Biol.* https://doi.org/10.1038/s41580-019-0177-4
10. Carlton, J.G., et al. 2012. *Science*. https://doi.org/10.1126/science.1217180
11. Dam, M., et al. 2025. *J. Cell Biol.* https://doi.org/10.1083/jcb.202502014
12. Singh, M.I., et al. 2025. *EMBO J.* https://doi.org/10.1038/s44318-025-00453-w
13. Petsalaki, E., et al. 2023. *J. Cell Biol.* https://doi.org/10.1083/jcb.202303123
14. Sadler, J.B.A., et al. 2018. *Proc. Natl. Acad. Sci. USA*. https://doi.org/10.1073/pnas.1805504115