DNA REPLICATION

Cohesin on the fork

> cohesin acetylation regulates replication fork progression.

Sister chromatid cohesion ensures proper chromosome segregation and is mediated by the cohesin complex forming a ring around sister chromatids. How DNA replication forks go through cohesin-associated obstructions to achieve genome replication remains unclear. Prasad Jallepalli and colleagues now report that fork advancement depends on cohesin acetylation, which might affect cohesin conformation.

Cohesion requires the acetylation of cohesin's structural maintenance of chromosomes 3 (SMC3) subunit, entrapment of nascent DNA strands in the cohesin ring and the chromosome transmission fidelity 18 -containing replication factor C complex (RFC^{CTF18}). To assess the contribution of RFC^{CTF18} to replication fork dynamics, the authors created RFC^{CTF18}-deficient human cells, pulse-labelled them with halogenated nucleosides (to label DNA) and used them for single-molecule analysis of DNA fibres. They found that lack of RFC^{CTF18} decreases fork velocity and increases fork density (owing to reactivation of dormant origins) and the frequency at which forks arrest or collapse. Importantly, loss of RFC^{CTF18} activity also leads to cohesion loss and premature chromatid separation.

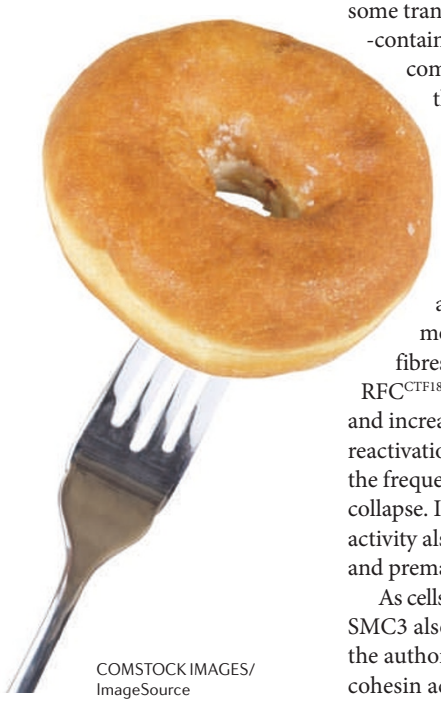
As cells expressing non-acetylatable SMC3 also show loss of cohesion, the authors investigated whether cohesin acetylation requires RFC^{CTF18}. Indeed, RFC^{CTF18}-deficient cells showed a 70% reduction of SMC3 acetylation. RFC^{CTF18} thus affects both replication fork processivity and cohesin acetylation, but are these processes linked?

Fork velocity is reduced in cells derived from patients with Roberts syndrome, who lack the SMC3-specific acetyltransferase ESCO2. Furthermore, fork speed is reduced in cells expressing non-acetylatable SMC3, suggesting that cohesin acetylation regulates replication fork progression.

But what is the mechanism by which cohesin acetylation promotes fork advancement? Acetylation promotes the dissociation of two cohesin cofactors — PDS5A and Wings apart-like (WAPL) — which regulate cohesin association with chromosomes. So, PDS5A and WAPL might keep cohesin in an occlusive conformation that is released by acetylation.

Together, these results show that RFC^{CTF18}-dependent cohesin acetylation is required to switch cohesin from a configuration that obstructs the fork to one that allows its advancement. Further studies are needed to clarify how this is regulated.

Kim Baumann



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ORIGINAL RESEARCH PAPER Terret, M.-E. *et al.* Cohesin acetylation speeds the replication fork. *Nature* 12 Nov 2009 (doi:10.1038/nature08550)
FURTHER READING Yanagida, M. Clearing the way for mitosis: is cohesin a target? *Nature Rev. Mol. Cell Biol.* **10**, 489–496 (2009)