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REPLICATION

Checkpoint tension relief

Transcription and DNA replication are coordinated, and replication forks are known to pause when they encounter a transcribing gene. Foiani and colleagues propose that the replication checkpoint may respond to such collisions by triggering the release of transcribed genes from the nuclear pore complex (NPC), thereby relieving topological tension on the DNA.

The integrity of replication forks is protected by the Mec1 (mitosis entry checkpoint 1) and Rad53 checkpoint, and cells with mutations in this checkpoint accumulate aberrant, or 'reversed', forks when exposed to hydroxyurea. The authors set out to test the hypothesis that these reversed forks arise from topological changes in the DNA. They screened a yeast deletion library for suppressors of the *rad53* mutant by testing for sensitivity to hydroxyurea and identified components of the THO and TREX2 complexes, as well as of the NPC. mRNA transcription is normally coupled to the mRNA export machinery through 'gene gating', in which the THO and TREX2 complexes and key nucleoporins couple transcribed genes to the NPC. So, the identification of THO, TREX2 and pore components in this screen raised the possibility that the NPC may affect replication by contributing to the formation of a topological barrier at the nuclear periphery.

The authors tested this model in several ways. First, they confirmed that mutants in Sac3, a component of the TREX2 complex, rescued the altered replicon dynamics in the *rad53* mutant and the accumulation of reversed forks. Moreover, whereas in wild-type cells exposure to hydroxyurea resulted in reduced association of transcribed galactose genes with the nuclear periphery, this release from the periphery did not occur in *rad53* mutants. So, engaging the Rad53 checkpoint seems to be required for redistribution of transcribing genes, perhaps through release from NPC association.

They further proposed that the checkpoint machinery may disrupt this barrier by targeting the NPC itself. The NPC component myosin-like protein 1 (Mlp1) is known to be phosphorylated by Rad53, and expression of a phosphomimic Mlp1 mutant could also rescue the hydroxyurea sensitivity of the *rad53* mutants, suggesting that Mlp1 is an important target for the protective effects of Rad53. Finally, they showed that physically introducing a double-strand break between a fork and a transcribed gene could also reduce fork reversal, consistent with the model that the checkpoint is acting to remove topological stress in the DNA.

On the basis of their results, Foiani and colleagues propose that Mec1 senses the tension that arises when a replication fork collides with genes being transcribed near the pore; this in turn may trigger Rad53-mediated phosphorylation of NPC components to allow gene release from the periphery, relief of topological tension and fork restart.

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ORIGINAL RESEARCH PAPER Bermejo, R. *et al.* The replication checkpoint protects fork stability by releasing transcribed genes from nuclear pores. *Cell* **146**, 233–246 (2011)
FURTHER READING Branzei, D. & Foiani, M. Maintaining genome stability at the replication fork. *Nature Rev. Mol. Cell Biol.* **11**, 208–219 (2010)

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