Nature Reviews Molecular Cell Biology | Published online 7 Mar 2018; doi:10.1038/nrm.2018.17

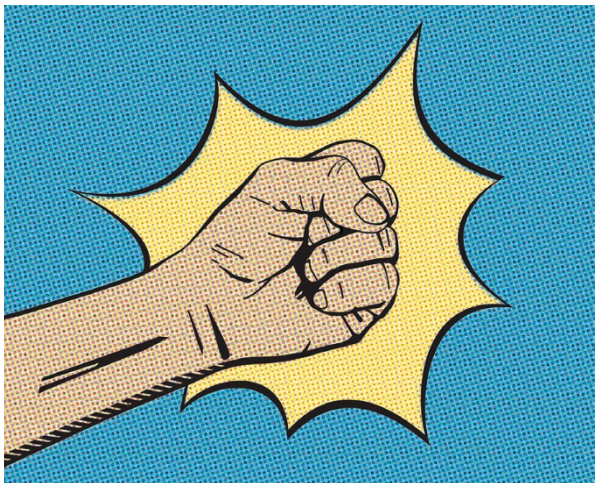
DNA REPLICATION

Onco-agent provocateur

Oncogene-induced replication stress (reduced replication-fork function and stability) contributes to cancer-associated genomic instability, but its molecular basis is poorly understood. Macheret and Halazonetis now show that oncogenes promote aberrant intragenic firing of replication origins, thereby causing transcription–replication conflicts and genome instability.

> “oncogene activation induced… origin firing at intragenic domains”

Human U2OS cells with inducible overexpression of the proto-oncogene cyclin E1 showed considerable shortening of the G1 phase of the cell cycle, as previously published. The authors identified >6,000 replication origins; ~1,000 of them were strongly induced in cyclin E1-overexpressing cells and termed oncogene-induced (Oi) origins.



S. Bradbrook/Macmillan Publishers Limited

Oi origins fired mainly in cells with the shortest G1 phases. Although constitutive origins mapped primarily to intergenic regions, many Oi origins — particularly those firing in early S phase — mapped to protein-coding genes, mostly at their 3′-ends. Thus, oncogene activation induced premature entry to S phase and origin firing at intragenic domains that are normally devoid of replication initiation.

The genic Oi origins mapped to highly transcribed regions, but transcription and replication measurements at large transcribed genes revealed that transcription had not yet reached the 3′-ends of the genes at the beginning of S phase. Furthermore, in cells expressing normal cyclin E1 levels, transcription inhibition during G1 resulted in intragenic origin firing at the same positions as the Oi origins. This suggested that transcription suppresses origin firing and that, upon oncogene-induced premature S phase entry, 3′-end intragenic origins fire because transcription does not have the time needed to reach their position.

As a measure of fork stability, examination of replication resumption following replication arrest revealed overall fork collapse at Oi origins. The degree of fork collapse correlated with transcription levels at the Oi origins, and inhibiting transcription rescued fork collapse. This indicated that transcription–replication conflicts were the underlying cause of fork collapse.

Finally, the authors investigated the formation of DNA double-strand break (DSB)-mediated chromosomal translocations with a CRISPR–Cas9-induced site-specific DSB. Upon cyclin E1 overexpression, translocation breakpoints were enriched at Oi origin domains, but only at highly-transcribed loci. Similar chromosomal rearrangement breaks were found in a large cohort of human cancers.

In summary, by causing both shortening of the G1 phase and origin firing at highly transcribed genes, oncogenes promote transcription–replication conflicts and cause replication stress and genome instability.

Eytan Zlotorynski

ORIGINAL ARTICLE Macheret, M & Halazonetis, T.D. Intragenic origins due to short G1 phases underlie oncogene-induced DNA replication stress. *Nature* https://doi.org/10.1038/nature25507 (2018)
FURTHER READING García-Muse, T. & Aguilera, A. Transcription–replication conflicts: how they occur and how they are resolved. *Nat. Rev. Mol. Cell Biol.* **17**, 553-563 (2016)