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Journal club

CONSERVATIVE DNA REPLICATION

The classic experiment described by Meselson and Stahl in their paper from 1958 demonstrated that genomes are replicated in a semiconservative manner. However, Donnianni and Symington, and Saini *et al.* have recently provided examples of conservative DNA replication in yeast cells.

DNA replication initiated from origins of replication proceeds in a semiconservative manner, such that each new copy of double-stranded DNA contains one original strand and one newly replicated strand (Meselson and Stahl). However, DNA replication can also be initiated, after DNA replication fork collapse, by break-induced replication (BIR; also known as recombination-restarted replication), as discussed by Anand and colleagues.

In BIR, homologous recombination leads to strand invasion, and then the invading strand acts as a primer for leading strand synthesis. Two recent papers from the laboratories of Symington (Donnianni and Symington) and Malkova (Saini *et al.*) have characterized BIR-initiated forks in budding yeast. Both laboratories show that the displacement loop (D-loop), which is formed during strand invasion, persists during replication and moves with the fork. Lagging synthesis occurs behind the D-loop. As the D-loop moves with the fork, the part of the leading strand that is behind the leading polymerase dissociates from the template DNA. The dissociated part of the leading strand is then copied by the lagging strand DNA polymerase. Thus, the template DNA retains its two original strands, whereas the copy contains the two newly synthesized strands.

> “Two recent papers… have characterized BIR-initiated forks in budding yeast”

This conservative mode of DNA replication must require a different set of proteins than those involved in semiconservative DNA replication. One such candidate is DNA polymerase δ subunit 3 (POLD3; encoded by *POL32* in budding yeast), which is dispensable for origin-initiated DNA replication but is required for BIR, as discussed by Anand and colleagues.

BIR probably evolved to enable the restart of collapsed DNA replication forks, apparently a rare event in normal cells. However, in cancer cells, collapsed replication forks are frequent and BIR is involved in their restart (Costantino *et al.*). Thus, if BIR is found to be conservative in humans, as it is in budding yeast, one could envisage that this would provide a myriad of new targets against which therapies for treating human cancers could be developed.

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