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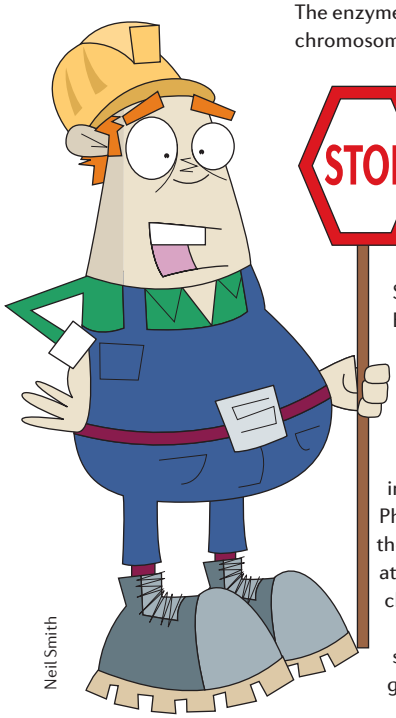
DNA DAMAGE RESPONSE

Keeping telomerase at bay



Neil Smith

The enzyme telomerase maintains chromosome integrity by synthesizing telomeres at chromosome ends. What prevents telomerase from adding telomeres to double-stranded DNA breaks (DSBs)? In *Nature Cell Biology*, Svetlana Makovets and Elizabeth Blackburn now report that DNA damage signalling induces phosphorylation of the telomerase inhibitor Pif1 (petite integration frequency 1). Phosphorylation of Pif1 blocks the activity of telomerase at DNA breaks but not at chromosome ends.

In budding yeast, DSBs sustained during normal growth or as a result of genotoxic stress activate the kinases Tel1 and Mec1 — orthologues of mammalian ATM (ataxia telangiectasia mutated) and ATR (ATM and Rad3-related), respectively — to induce phosphorylation of the checkpoint kinases Chk1 and Rad53. Makovets and Blackburn found that Pif1, which is known to antagonize telomerase function at DNA ends, is phosphorylated following DNA damage. Deletion of *MEC1* or *RAD53* blocks DNA damage-induced Pif1 phosphorylation, although Rad53 is not required for the recruitment of Pif1 to DSBs. These data indicate that the DNA damage response pathway regulates Pif1 phosphorylation but not Pif1 localization.

Intriguingly, expression of a Pif1 mutant that cannot be phosphorylated at Thr763, Ser765, Ser766 or Ser769 (*pif1-4A*) allows the erroneous addition of telomeres at DSBs; the same effect was observed in *PIF1*-null cells. By contrast, *pif1-4A* has no effect on telomere addition at natural chromosome ends. Phosphorylation of Pif1 is not induced by stalled replication forks or by nocodazole-mediated mitotic arrest. Thus, Mec1-dependent phosphorylation of Pif1 between residues 763–769 is activated specifically in response to DNA breaks, and this potentiates its ability to inhibit telomerase activity at DSBs.

Additional experiments reveal that DSBs induce Pif1 phosphorylation at Thr763 and Ser766, which is essential for the restraint of telomerase function at DSBs. However, it is not yet known how the phosphorylation of Pif1 blocks telomerase activity at these sites. It is also important to elucidate whether Pif1 is a direct target of Rad53 and Dun1 (a kinase downstream of Rad53), and whether this pathway is conserved in mammalian cells.

Emily J. Chenette, Associate Editor,
UCSD-Nature Signaling Gateway

ORIGINAL RESEARCH PAPER Makovets, S. & Blackburn, E. H. DNA damage signalling prevents deleterious telomere addition at DNA breaks. *Nature Cell Biol.* **11**, 1383–1386 (2009).