DEFINING THE ROLE OF SMARCAL1

AT ALTERNATIVELY-LENGTHENED TELOMERES

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ABSTRACT

Cellular immortalization is a prerequisite of cancers and depends upon evasion of telomeric erosion that would otherwise lead to replicative senescence. A subset of cancers achieves telomere maintenance via a pathway known as Alternative Lengthening of Telomeres (ALT), which relies on homologous recombination that is driven by chronic DNA replication stress and allows for telomeric elongation events. Here, we sought to further elucidate the role of the annealing helicase SMARCAL1, which reverses and stabilizes stalled replication forks, in cancers that utilize ALT. SMARCAL1 is crucial to resolve the replication stress at ALT telomeres, but paradoxically is lost in a subset of ALT-positive tumors. Other common ALT-related mutations occur in the ATRX/DAXX complex, which deposits the histone variant H3.3 at telomeres. In contrast to loss of ATRX, we found that SMARCAL1 depletion does not affect H3.3 deposition, but does lead to changes in trimethylation of histone 3 lysine 9 that may create an ALT-permissive state. We also found that ALT-positive cell lines are more sensitive to combined depletion of SMARCAL1 and ATRX. Furthermore, we discovered that SMARCAL1 interacts with heterochromatin protein 1 (HP1), and that loss of SMARCAL1 deregulates the presence of HP1 at telomeres, providing a link to changes in histone methylation. We also identified a novel complex between SMARCAL1, HP1, and the histone methyltransferase

SETDB1. Overall, our results indicate that SMARCAL1 is an important factor in telomeric chromatin formation, indicating a previously undescribed role for SMARCAL1 in genome maintenance.