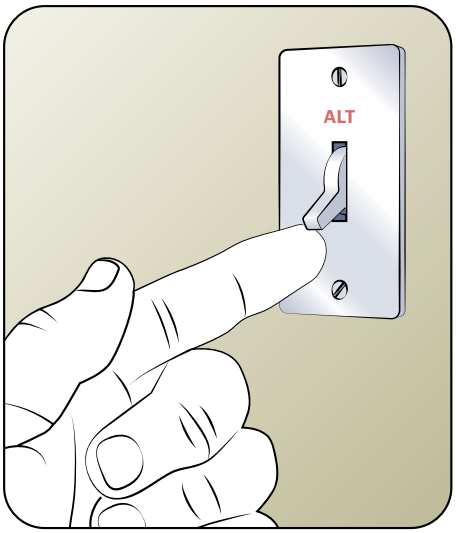
Cancer genomics

Switching on cancer survival mechanisms



To escape proliferative arrest, cancer cells must protect against the telomere shortening that accompanies DNA replication. Approximately 10% of cancer cells use a recombination-dependent pathway known as alternative lengthening of telomeres (ALT) for maintaining telomere length. However, the mechanism that leads to the activation of the ALT pathway remains largely unknown.

Cancer cells that employ ALT often harbour loss-of-function mutations in the gene encoding ATRX, a chromatin remodelling protein, indicating that ATRX normally supresses ALT. To test this hypothesis, Turkalo and Maffia et al. knocked out the *ATRX* gene in human pluripotent stem cells lacking the checkpoint proteins p14 and p16, which undergo uncontrolled proliferation. In the proliferative state, loss of ATRX did not result in any observable ALT phenotype; however, the differentiation of ATRX-deficient cells into fibroblasts induced the molecular hallmarks of ALT, including telomeric DNA synthesis outside of S phase, formation of ALT-associated promyelocytic leukaemia bodies (APBs) and long and heterogenous telomeres. These findings suggest that loss of ATRX induces ALT in a cell-state-specific manner.

The finding that differentiation acts as a switch to induce ALT contrasts with the prevailing view that ALT occurs when telomeres become critically short — a state known as telomere crisis. To test this hypothesis, the authors used a system to tightly control the onset of telomere crisis by disrupting the telomerase complex. These experiments revealed that induction of telomere crisis did not lead to the development of ALT and that differentiation of these cells into fibroblasts or neuronal precursor cells was essential for ALT activation. Thus, telomere truncation and crisis are not sufficient to trigger ALT.

The authors next probed the functional consequences of the activation of ALT in ATRX-null cells. Whereas *ATRX*-positive cells failed to immortalize when continually passaged in either their undifferentiated or differentiated state, differentiated cultures arising from ATRX-deficient stem cells continued to proliferate, resulting in functionally immortal cells.

Finally, the authors sequenced the template strands of individual ATRX-deficient cells using Strand-seq to gain insight into the genetic mechanisms of ALT. Strand-seq showed that activation of ALT following differentiation promotes genomic rearrangements and that differentiated ATRX-deficient clones undergo telomere recombination, resulting in telomere-to-telomere fusion. Thus, these data provide unique insight into the genetic basis of ALT.

Overall, these findings show that loss of *ATRX* followed by a non-genetic switch that can be triggered by differentiation induces ALT and immortalizes cells. Future research is needed to identify the mechanisms by which differentiation triggers ALT, and to understand why proliferating cells do not undergo ALT even when lacking ATRX.

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Original article: Turkalo, T. K. et al. A non-genetic switch triggers alternative telomere lengthening and cellular immortalization in ATRX deficient cells. *Nat. Commun.* **14**, 939 (2023)

Related article: Gao, J. & Pickett, H. A. Targeting telomeres: advances in telomere maintenance mechanism-specific cancer therapies. *Nat. Rev. Cancer* **22**, 515–532 (2022)

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