Epigenetic Regulation of Alternative Lengthening of Telomeres (ALT) in Cancer: Implications for Therapeutic Targeting

Tsai Chia-Tsen
Molecular and Cellular Biology Institution in Academia Sinica, Taipei, Taiwan

Chen Liuh-Yow
Molecular and Cellular Biology Institution in Academia Sinica, Taipei, Taiwan

Abstract

Telomeres protect chromosomes from damage but shorten with each cell division, eventually leading to cellular senescence. While most cancer cells maintain telomere length through telomerase reactivation, approximately 10-15% of cancers employ an alternative mechanism called Alternative Lengthening of Telomeres (ALT). ALT utilizes homologous recombination to extend telomeres without telomerase. However, the molecular mechanisms that govern the induction of ALT remain poorly understood, hindering the development of targeted therapies.

Our previous work demonstrated that tethering orphan nuclear receptors (NRs) to non-ALT telomeres can induce ALT-like phenotypes, although the underlying mechanism remained unclear. In this study, we uncover that orphan NRs regulate ALT induction in a TRIM28-dependent manner. We show that these receptors recruit TRIM28 to telomeres, enhancing the deposition of H3K9me3, a key epigenetic modification, and promoting the formation of ALT-associated phenotypes. Interestingly, our findings suggest that telomeric epigenetic modifications, such as H3K9me3, can trigger ALT under specific conditions.

These results provide new insights into the regulation of ALT and highlight the potential of targeting epigenetic regulators like TRIM28 and orphan NRs as therapeutic strategies for ALT-positive cancers, offering a pathway for precision cancer treatments.