ACHIEVEMENTS

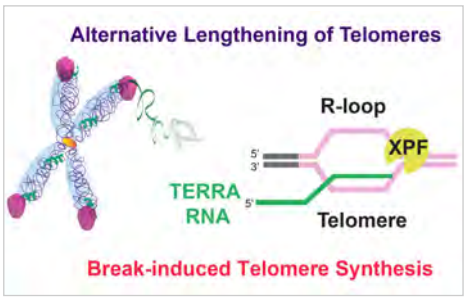
Breaks before Synthesis - New Insights into ALT Cancer Therapy

Maintenance of telomere length is closely related to processes of cancers and aging. How do telomeres extend in length? It is well-known that the telomerase enzyme can lengthen telomeres. However, some cancers do not depend on telomerase activity to lengthen their telomeres. Instead, they utilize "Alternative lengthening of Telomeres (ALT)," a mechanism that includes a break-induced replication to extend telomeres and is highly conserved in many eukaryotes. Patients with ALT cancers have a higher mortality rate than those with non-ALT cancers.

How do cells initiate the breaks of telomeres? Dr. Hsueh-Ping (Catherine) Chu's research team at NTU's Institute of Molecular and Cellular Biology discovered that TERRA R-loops and XPF are the drivers. TERRA is a long non-coding RNA, which contains telomeric repeat sequences and forms DNA:RNA hybrids at telomeres. The DNA:RNA hybrid and a displaced single-stranded DNA form an R-loop structure. The enrichment of TERRA R-loops was observed in cancer cells utilizing the ALT mechanism. The research team also disclosed that TERRA R-loops trigger telomere clustering and activate DNA damage response by recruiting XPF. Such DNA damage response at telomeres is required for inducing homologous recombination and telomere synthesis in ALT cancer cells.

Ph.D. student Hong-Jhih Shen developed an RCas9 system to deplete TERRA RNA without editing telomeric DNA in ALT cells, finding that TERRA depletion shortens telomere length in ALT cancer cells. Ph.D. student Chia-Yu Guh identified TERRA interacting proteins in ALT cells, revealing that TERRA interacts with a large subset of proteins involved in the DNA repair pathway. Interestingly, TERRA interacts with several nucleotide excision repair factors, including XPF, an enzyme that cuts DNA. Postdoctoral Research Fellow Liv Weichien Chen and graduate student Pei-Chen Chiu showed that TERRA R-loops recruit XPF to telomeres, leading to DNA double-strand breaks to activate break-induced telomere synthesis.

Targeting XPF by small interference RNAs inhibits cell growth in ALT cancer cells and reduces telomere lengthening. These findings provide new insights into ALT cancer therapy.



TERRA is a non-coding RNA which is transcribed from the ends of chromosomes and forms an R-loop with telomeric DNA. TERRA R-loops recruit XPF, an enzyme that cuts DNA to induce DNA synthesis to extend telomeres and drive Alternative Lengthening of Telomeres.

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